Supplementry Information
for

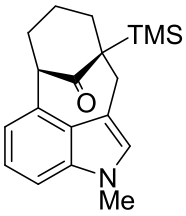
Bridgehead Enolates and Bridgehead Alkenes in a Welwistatin Model Series

Valerie Boissel, Nigel S. Simpkins, Gurdip Bhalay, Alexander J. Blake, and William Lewis

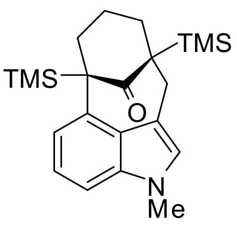
School of Chemistry, The University of Birmingham, Edgbaston, Birmingham, B15 2TT U.K., School of Chemistry, The University of Nottingham, University Park, Nottingham NG7 2RD U.K., and Novartis, Horsham Research Centre, West Sussex, RH12 5AB U.K.

Contents

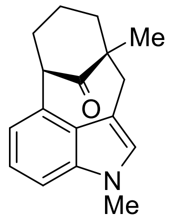
General Procedures: All reactions were carried out in dry solvents under an atmosphere of argon. THF was freshly distilled from sodium benzophenone and dichloromethane (DCM) from CaH_2. All other reagents were used as received from commercial suppliers unless otherwise stated. Commercially available LiI (anhydrous) was dried under high vacuum ($T_{oil\ bath}$ = 80 °C) for 4 h. All electrophiles (prenylBr, BnBr, PhCHO, TMSCl) were distilled prior to use except for commercial methyl iodide and methyl chloroformate which were used without further purification. All yields are isolated yields after purification by column chromatography, except where stated. Melting points were obtained using a standard hotplate apparatus and are uncorrected. Infrared spectra were recorded using an FTIR spectrophotometer as sample solutions in chloroform or as KBr films and are reported in cm^{-1}. High resolution mass spectra were acquired using a TOF mass spectrometer, using electrospray ionisation (ESI) unless stated otherwise. ^1H and ^{13}C NMR spectra were recorded at 300, 400 or 500 MHz, using $CDCl_3$ as solvent, and calibrated on residual solvents signals. *J* values are recorded in Hz and quoted to the nearest 0.1. Reaction progress was monitored by thin layer chromatography (TLC) and plates were visualized under UV light or by development using *p*-anisaldehyde. Flash column chromatography was performed using the indicated solvent systems and commercial Davisil silica gel 60A (35-70μ).



Bridgehead monosilylated product 3 (Scheme 1). A solution of LTMP (0.21 mmol, 1.0 eq), cooled to -78 °C was added dropwise *via* cannula to a solution of ketone **2** (50 mg, 0.21 mmol) and TMSCl (0.30 mL, 2.1 mmol, 10 eq) in THF (2 mL), maintained at that temperature. The resulting solution was allowed to warm slowly to room temperature over 12 h, quenched with saturated aqueous NH_4Cl (5 mL) and extracted with ether (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (light petroleum/ethyl acetate = 95:5) to give the desired product **3** as a colourless solid (43.6 mg, 56%). R_f 0.73 [light petroleum/ethyl acetate (80:20)]. mp 111-114 °C. IR υ_{max} 2951, 1679, 1446, 1316 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 9 H), 1.34 (m, 1 H), 1.47 (m, 1 H), 1.84 (m, 1 H), 1.91-2.00 (m, 2 H), 2.10 (m, 1 H), 2.92 (d, 1 H, *J* = 15.4 Hz), 3.13 (d, 1 H, *J* = 15.4 Hz), 3.74 (s, 3 H), 4.01 (m, 1 H), 6.87 (dd, 1 H, J = 5.5, 2.2 Hz), overlapping 6.89 (s, 1 H), 7.14-7.21 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ -2.7 (**C**H_3), 18.8 (**C**H_2), 32.7 (**C**H_3), 33.0 (**C**H_2), 33.2 (**C**H_2), 35.9 (**C**H_2), 42.4 (**C**), 58.4 (**C**H), 107.3 (**C**H), 113.5 (**C**), 118.2 (**C**H), 121.8 (**C**H), 126.5 (**C**H), 127.4 (**C**), 133.5 (**C**), 137.0 (**C**), 218.1 (**C**). HRMS (ESI) *m/z* 334.1585 $[M+Na]^+$, $[C_{19}H_{25}NOSiNa]^+$ requires 334.1598.

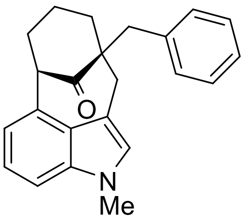


Bridgehead disilylated product 4 (Scheme 1). A solution of LTMP (1.04 mmol, 5.0 eq), cooled to -78 °C was added dropwise *via* cannula to a solution of ketone **2** (50 mg, 0.21 mmol) and TMSCl (0.30 mL, 2.1 mmol, 10 eq) in THF (2 mL), maintained at that temperature. The resulting solution was allowed to warm slowly to room temperature over 4 h, quenched with saturated aqueous NH$_4$Cl (5 mL) and extracted with ether (3 x 5 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (light petroleum/ethyl acetate = 95:5) to give the desired product **3** as a colourless solid (55.0 mg, 68%). R$_f$ 0.52 [light petroleum/ethyl acetate (95:5)]. mp 145-146 °C. IR υ_{max} 2950, 2902, 1655, 1317, 1110 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.17 (s, 9 H), 0.28 (s, 9 H), 1.36 (dm, 1 H, *J* = 13.2 Hz), 1.52 (dm, 1 H, *J* = 13.2 Hz), 1.83 (dm, 1 H, *J* = 12.0 Hz), 1.97-2.02 (m, 2 H), 2.09 (m, 1 H), 2.82 (d, 1 H, *J* = 15.2 Hz), 3.29 (d, 1 H, *J* = 15.2 Hz), 3.70 (s, 3 H), 6.87 (br. s, 1 H), 7.08 (m, 1 H), 7.08-7.17 (m, 2 H). ^{13}C NMR (100 MHz, CDCl$_3$) δ -2.2 (**C**H$_3$), 0.6 (**C**H$_3$), 19.0 (**C**H$_2$), 32.8 (**C**H$_3$), 33.1 (**C**H$_2$), 35.0 (**C**H$_2$), 37.5 (**C**H$_2$), 43.3 (**C**), 54.1 (**C**), 107.0 (**C**H), 114.2 (**C**), 117.9 (**C**H), 121.4 (**C**H), 126.4 (**C**H), 128.8 (**C**), 137.4 (**C**), 137.8 (**C**), 221.9 (**C**). HRMS (ESI) *m/z* 406.1991 [M+Na]$^+$, [C$_{22}$H$_{32}$NOSi$_2$Na]$^+$ requires 406.1993.

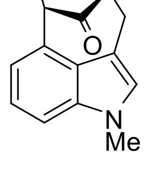


Compound 5. A solution of lithium amide base was prepared as previously described; TMP (675 μL, 4.0 mmol), in dry THF (4.8 mL) at -78 °C, with ^{n}BuLi (1.60 mol.L^{-1} solution in hexanes; 2.50 mL, 4.0 mmol). The solution was allowed to warm to 0 °C. After 10 min, it was re-cooled to -78 °C before 1.67 mL of this LTMP solution (0.5 M in THF, 0.837 mmol, 2.0 eq) was slowly added to a solution of ketone **2** (100 mg, 0.418 mmol) in dry THF (6 mL). The resulting solution was stirred at -78 °C for 0.5 h. Then MeI (260 μL, 4.18 mmol, 10.0 eq) was added dropwise and the reaction mixture stirred for 1 h at -78 °C then 1 h at room temperature. The solution was subsequently quenched with saturated aqueous NH$_4$Cl (20 mL) and extracted with ether (3 x 20 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (light petroleum/ethyl acetate = 95:5) to give the desired product **5** as a colourless solid (76.4 mg, 72%) along with unreacted starting material (20.0 mg, 20%). R$_f$ 0.54 [light petroleum/ethyl acetate (80:20)]. mp 96-99 °C. IR υ_{max} 2930, 1694, 1458, 1375, 1322, 1101 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.30 (s, 3 H), 1.35 (m, 1 H), 1.59 (m, 1H), 1.84 (ddd, 1 H, *J* = 13.5, 8.6, 4.8 Hz), 1.94 (dm, 1 H,

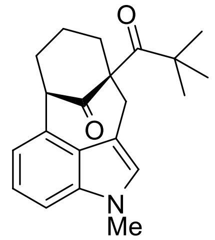
J = 13.1 Hz), 2.07 (dm, 1 H, J = 13.6 Hz), 2.19 (m, 1H), 2.83 (d, 1 H, J = 15.8 Hz), 2.90 (d, 1 H, J = 15.7 Hz), 3.74 (s, 3 H), 4.11 (m, 1 H), 6.87-6.90 (m, 2 H), 7.13-7.22 (m, 2 H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 19.6 (**C**H$_2$), 28.2 (**C**H$_3$), 32.8 (**C**H$_3$), 37.7 (**C**H$_2$), 40.0 (**C**H$_2$), 40.9 (**C**H$_2$), 48.2 (**C**), 58.1 (**C**H), 107.4 (**C**H), 112.2 (**C**), 118.3 (**C**H), 122.1 (**C**H), 126.5 (**C**H), 127.1 (**C**), 133.3 (**C**), 137.0 (**C**), 216.1 (**C**). HRMS (ESI) *m/z* 254.1548 [M+H]$^+$, [C$_{18}$H$_{19}$NO]$^+$ requires 254.1545.



Compound 6. A solution of lithium amide base was prepared as previously described; TMP (675 µL, 4.0 mmol), in dry THF (4.8 mL) at -78 °C, with ^{n}BuLi (1.60 mol.L^{-1} solution in hexanes; 2.50 mL, 4.0 mmol). The solution was allowed to warm to 0 °C. After 10 min, it was re-cooled to -78 °C before 1.67 mL of this LTMP solution (0.5 M in THF, 0.837 mmol, 2.0 eq) was slowly added to a solution of ketone **2** (100 mg, 0.418 mmol) in dry THF (6 mL). The resulting solution was stirred at -78 °C for 0.5 h. Then freshly distilled BnBr (500 µL, 4.18 mmol, 10.0 eq) was added dropwise and the reaction mixture stirred for 1 h at -78 °C then 1 h at room temperature. The solution was subsequently quenched with saturated aqueous NH$_4$Cl (20 mL) and extracted with ether (3 x 25 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (light petroleum/ethyl acetate = 95:5) to give the product **6** as a colourless solid (101.1 mg, 73%) along with unreacted starting material (16.0 mg, 16%). R$_f$ 0.44 [light petroleum/ethyl acetate (80:20)]. mp 153-157 °C. Found C, 83.98; H, 7.18; N, 4.37; C$_{23}$H$_{23}$NO requires C, 83.85; H, 7.04; N, 4.25. IR υ_{max} 2933, 1697, 1456, 1321, 1102, 1088 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.30 (m, 1 H), 1.48 (m, 1 H), 1.80-1.92 (m, 2 H), 1.96-2.11 (m, 2 H), 2.90-2.91 (br. d, 2 H, , J = 1.9 Hz), 2.98 (d, 1 H, , J = 13.6 Hz), 3.26 (d, 1 H, , J = 13.6 Hz), 3.71 (s, 3 H), 4.13 (m, 1 H), 6.84 (s, 1 H), 6.88 (dd, 1 H, J = 6.3, 1.8 Hz), 7.14-7.19 (m, 2 H), 7.25-7.34 (m, 5 H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 18.0 (**C**H$_2$), 32.6 (**C**H$_3$), 36.2 (**C**H$_2$), 36.3 (**C**H$_2$), 37.7 (**C**H$_2$), 45.2 (**C**H$_2$), 51.7 (**C**), 57.6 (**C**H), 107.2 (**C**H), 111.5 (**C**), 118.0 (**C**H), 121.8 (**C**H), 126.1 (**C**H), 126.6 (**C**H), 126.7 (**C**H), 127.6 (**C**H), 127.9 (**C**H), 131.1 (**C**H), 133.2 (**C**), 136.7 (**C**), 138.5 (**C**), 215.0 (**C**). HRMS (ESI) *m/z* 330.1852 [M+H]$^+$, [C$_{23}$H$_{24}$NO]$^+$ requires 330.1858.

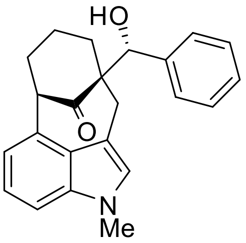


Compound 7. A solution of lithium amide base was prepared as previously described; TMP (675 µL, 4.0 mmol), in dry THF (4.8 mL) at -78 °C, with ^{n}BuLi (1.60 mol.L^{-1} solution in hexanes; 2.50 mL, 4.0 mmol). The solution was allowed to warm to 0 °C. After 10 min, it was re-cooled to -78 °C before 1.67 mL of this LTMP solution (0.5 M in THF, 0.836 mmol, 2.0 eq) was added dropwise to a solution of ketone **2** (100 mg, 0.418 mmol) in dry THF (6 mL) at -78 °C. The resulting solution was stirred at that maintained temperature for 0.5 h before being quenched slowly with freshly distilled prenyl bromide (483 µL, 4.18 mmol, 10.0 eq). The resulting solution was stirred 1 h at -78 °C then 1 h at room temperature. The reaction mixture was subsequently quenched with saturated aqueous NH_4Cl (20 mL) and extracted with ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (light petroleum/ethyl acetate = 95:5) to give the desired product **7** as a colourless oil (72.7 mg, 57%). R_f 0.73 [light petroleum/ethyl acetate (80:20)]. IR υ_{max} 2928, 1697, 1606, 1457, 1377, 1321, 1084 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (m, 1 H), 1.54 (m, 1 H), 1.70 (s, 3 H), 1.79 (s, 3 H), 1.91-1.97 (m, 3 H), 2.14 (m, 1 H), 2.39 (dd, 1H, *J* = 14.2, 8.8 Hz), 2.49 (dd, 1 H, *J* = 14.2, 5.9 Hz), 2.78 (d, 1 H, *J* = 15.6 Hz), 2.97 (d, 1 H, *J* = 15.6 Hz), 3.74 (s, 3H), 4.11 (m, 1 H), 5.23 (m, 1 H), 6.88-6.93 (m, 2 H), 7.16-7.22 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1 (2 x **C**H_3), 19.3 (**C**H_2), 26.2 (**C**H_3), 32.7 (**C**H_3), 36.5 (**C**H_2), 36.6 (**C**H_2), 37.8 (**C**H_2), 38.6 (**C**H_2), 51.7 (**C**), 57.9 (**C**H), 107.3 (**C**H), 112.0 (**C**), 118.1 (**C**H), 120.7 (**C**H), 121.9 (**C**H), 126.6 (**C**H), 127.1 (**C**), 133.3 (**C**), 134.1 (**C**), 136.9 (**C**), 215.6 (**C**). HRMS (ESI) *m/z* 308.2010 $[M+H]^+$, $[C_{21}H_{26}NO]^+$ requires 308.2014.

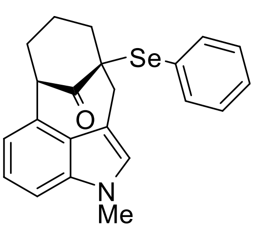


Compound 8. A solution of lithium amide base was prepared as previously described; TMP (372 µL, 2.2 mmol), in dry THF (2.4 mL) at -78 °C, with ^{n}BuLi (1.60 mol.L^{-1} solution in hexanes; 1.25 mL, 2.0 mmol). The solution was allowed to warm to 0 °C. After 10 min, it was re-cooled to -78 °C before 3.34 mL of this LTMP solution (0.5 M in THF, 1.68 mmol, 2.0 eq) was slowly added to a solution of ketone **2** (200 mg, 0.84 mmol) in dry THF (12 mL). The resulting solution was stirred at -78 °C for 1 h. Then trimethylacetylchloride (308 µL, 2.52 mmol, 3.0 eq) was added in one pot and the reaction mixture stirred for 1 h at -78 °C then 1 h at room temperature. The solution was subsequently quenched with saturated aqueous NH_4Cl (20 mL) and extracted with ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (light petroleum/ethyl acetate = 90:10) to give the desired product **8** as a colourless solid (235.3 mg, 85%). R_f 0.37 [light petroleum/ethyl acetate (80:20)]. mp 151-155 °C. Found C, 78.06; H, 7.89; N, 4.45; $C_{21}H_{25}NO_2$ requires C, 77.98; H, 7.79; N, 4.33. IR υ_{max} 2935, 2868, 1694, 1456, 1321, 1081 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 9 H), 1.82-1.87 (m, 2 H), 1.94-1.99 (m, 2 H), 2.42 (m, 1 H), 2.51 (m, 1 H), 3.06 (dm, 1 H, *J* = 15.9 Hz), 3.29 (d, 1 H, *J* =

15.9 Hz), 3.74 (s, 3 H), 4.22 (m,1 H), 6.92 (m, 1 H), 6.97 (d, 1 H, *J* = 1.3 Hz), 7.17-7.19 (m, 2 H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 18.1 (**C**H$_2$), 29.8 (3 x **C**H$_3$), 32.8 (**C**H$_3$), 33.3 (**C**H$_2$), 34.5 (**C**H$_2$), 36.0 (**C**H$_2$), 45.0 (**C**), 56.2 (**C**H), 64.5 (**C**), 107.8 (**C**H), 110.5 (**C**), 118.2 (**C**H), 121.9 (**C**H), 127.0 (**C**), 127.8 (**C**H), 132.8 (**C**), 137.0 (**C**), 212.9 (**C**), 214.3 (**C**). HRMS (ESI) *m/z* 324.1966 [M+H]$^+$, [C$_{21}$H$_{26}$NO$_2$]$^+$ requires 324.1964.

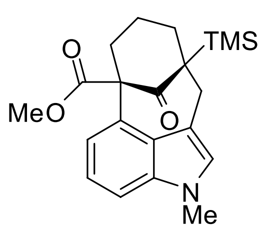


Compound 9. A solution of lithium amide base was prepared as previously described; TMP (675 µL, 4.0 mmol), in dry THF (4.8 mL) at -78 °C, with ^{n}BuLi (1.60 mol.L^{-1} solution in hexanes; 2.50 mL, 4.0 mmol). The solution was allowed to warm to 0 °C. After 10 min, it was re-cooled to -78 °C before 1.67 mL of this LTMP solution (0.5 M in THF, 0.836 mmol, 2.0 eq) was slowly added to a solution of ketone **2** (100 mg, 0.418 mmol) in dry THF (6 mL). The resulting solution was stirred at -78 °C for 0.5 h. Then freshly distilled PhCHO (85 µL, 0.837 mmol, 2.0 eq) was added dropwise and the reaction mixture stirred for 10 min at -78 °C before being subsequently quenched with saturated aqueous NH$_4$Cl (10 mL) and extracted with ether (3 x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (light petroleum/ethyl acetate = 80:20) to give the product **9** as a single diastereomer (73.1 mg, 51%). R$_f$ 0.41 [light petroleum/ethyl acetate (80:20)]. mp 86-89 °C. IR υ_{max} 3471, 2940, 1682, 1453, 1323, 1282, 1098, 1048 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.34-1.50 (m, 3 H), 1.82 (m, 1 H), 1.96 (m, 1 H), 2.18 (m, 1 H), 2.81 (d, 1 H, *J* = 16.2 Hz), overlapping 3.73 (m, 1 H), 3.74 (s, 3 H), 4.18 (m, 1 H), 5.06-5.09 (m, 2 H), 6.88 (dd, 1 H, *J* = 5.6, 3.0 Hz), 6.92 (br. s, 1 H), 7.18-7.20 (m, 2 H), 7.32-7.40 (m, 3 H), 7.46-7.49 (m, 2 H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 18.7 (**C**H$_2$), 27.8 (**C**H$_2$), 32.6 (**C**H$_3$), 37.0 (**C**H$_2$), 37.7 (**C**H$_2$), 54.2 (**C**), 58.6 (**C**H), 79.4 (**C**H), 107.5 (**C**H), 111.2 (**C**), 117.9 (**C**H), 121.8 (**C**H), 126.4 (**C**), 127.3 (**C**H), 127.6 (2 x **C**H), 128.6 (2 x **C**H), 132.1 (**C**), 136.7 (**C**), 139.0 (**C**), 220.1 (**C**). HRMS (ESI) *m/z* 368.1620 [M+Na]$^+$, [C$_{23}$H$_{23}$NNaO$_2$]$^+$ requires 368.1626.



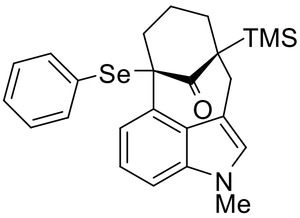
Compound 10. A solution of lithium amide base was prepared as previously described; TMP (675 µL, 4.0 mmol), in dry THF (4.8 mL) at -78 °C, with ^{n}BuLi (1.60 mol.L^{-1} solution in hexanes; 2.50 mL, 4.0 mmol). The solution was allowed to warm to 0 °C. After 10 min, it was re-cooled to -78 °C. An oven-dried round-bottom flask,

purged with argon, was charged with the substrate **2** (100 mg, 0.418 mmol) in dry THF (6 mL). A freshly prepared solution of LTMP (1.67 mL, 3.18 mmol, 2.0 eq) was added dropwise at a maintained -78 °C over 15 min and the resultant mixture was stirred at that temperature for 0.5 h. Then PhSeSePh (392 mg, 1.26 mmol, 3.0 eq) was dissolved in dry THF (1 mL) and added dropwise to the mixture. The solution was subsequently stirred 1 h at -78 °C then 1 h at room temperature before being quenched by saturated aqueous NH_4Cl (20 mL). The aqueous phase was extracted with ether (3 x 20 mL) and the organic layers combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified *via* column chromatography (light petroleum/ethyl acetate = 90:10) to afford the desired product **10** as a colourless solid (146.0 mg, 88%). R_f = 0.34 [light petroleum/ethyl acetate (90:10)]. mp 177-179 °C. IR (KBr film) υ_{max} 2919, 1690, 1459, 1323, 1227, 1084, 742, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31-1.50 (m, 2 H), 1.93 (m, 1 H), 2.09 (m, 1 H), 2.23 (m, 1 H), 2.43 (m, 1 H), 2.32 (d, 1 H, *J* = 15.5 Hz), 3.55 (dm, 1 H, *J* = 15.4 Hz), 3.72 (s, 3 H), 4.27 (m, 1 H), 6.86 (d, 1 H, *J* = 1.1 Hz), 6.89 (dd, 1 H, *J* = 6.3, 1.5 Hz), 7.14-7.22 (m, 2 H), 7.33-7.45 (m, 3 H), 7.76-7.79 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (**C**H_2), 32.7 (**C**H_3), 36.5 (**C**H_2), 39.4 (**C**H_2), 40.6 (**C**H_2), 58.1 (**C**H), 61.1 (**C**), 107.5 (**C**H), 111.4 (**C**), 118.3 (**C**H), 122.1 (**C**H), 126.5 (**C**H), 126.6 (**C**), 128.2 (**C**), 128.76 (2 x **C**H), 128.80 (**C**H), 132.4 (**C**), 136.9 (**C**), 138.5 (2 x **C**H), 211.7 (**C**). HRMS (ESI) *m/z* 418.0684 $[M+Na]^+$, $[C_{22}H_{21}NO^{80}SeNa]^+$ requires 418.0686.

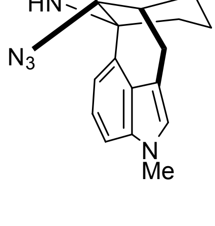


Compound 11. A solution of lithium amide base was prepared as previously described; TMP (1.4 mL, 8.0 mmol), in dry THF (9.7 mL) at -78 °C, with ^{n}BuLi (1.60 mol.L^{-1} solution in hexanes; 5.0 mL, 8.0 mmol). The solution was allowed to warm to 0 °C. After 10 min, it was re-cooled to -78 °C before 12.9 mL of this LTMP solution (0.5 M in THF, 6.4 mmol, 2.0 eq) was slowly added to a solution of substrate **3** (1.0 g, 3.2 mmol) in dry THF (60 mL). The resulting solution was stirred at -78 °C for 1 h. Then methylchloroformate (745 µL, 9.7 mmol, 3.0 eq) was added in one pot and the reaction mixture stirred for 1 h at -78 °C then 1 h at room temperature. The solution was subsequently quenched with saturated aqueous NH_4Cl (40 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (light petroleum/ethyl acetate = 90:10) to give the desired product **11** as a yellow solid (692 mg, 58%, 91% brsm). R_f 0.32 [light petroleum/ethyl acetate (90:10)]. mp 110-113 °C. IR υ_{max} 2952, 1728, 1682, 1610, 1458, 1055 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 9 H), 1.24 (m, 1 H), 1.43 (m, 1 H), 1.75 (m, 1 H), 2.03 (m, 1 H), 2.14 (dm, 1 H, *J* = 13.4 Hz), 2.60 (ddd, 1 H, *J* = 13.4, 9.7, 3.7 Hz), 2.91 (d, 1 H, *J* = 15.5 Hz), 3.16 (d, 1 H, *J* = 15.4 Hz), 3.75 (s, 3 H), 3.85 (s, 3 H), 6.73 (m, 1 H), 6.93 (br. s, 1 H), 7.19-7.21 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -2.8 (**C**H_3), 19.3 (**C**H_2), 31.8 (**C**H_2), 32.7 (**C**H_3), 33.5 (**C**H_2), 38.5 (**C**H_2), 43.2 (**C**), 52.4 (**C**H_3), 70.2 (**C**), 107.8 (**C**H), 112.5 (**C**), 118.3 (**C**H), 121.5

(**C**H), 127.2 (**C**H), 127.6 (**C**), 131.9 (**C**), 137.1 (**C**), 173.6 (**C**), 213.9 (**C**). HRMS (ESI) *m/z* 370.1811 $[M+H]^+$, $[C_{21}H_{28}NO_3Si]^+$ requires 370.1838.



Compound 12. A solution of lithium amide base was prepared as previously described; TMP (1.12 mL, 6.6 mmol), in dry THF (7.1 mL) at -78°C, with ^{n}BuLi (1.60 mol.L^{-1} solution in hexanes; 3.76 mL, 6.0 mmol). The solution was allowed to warm to 0 °C. After 10 min, it was re-cooled to -78 °C. An oven-dried round-bottom flask, purged with argon, was charged with the substrate **3** (495 mg, 1.59 mmol) in dry THF (28 mL). A freshly prepared solution of LTMP (6.40 mL, 3.18 mmol, 2.0 eq) was added dropwise at a maintained -78 °C over 15 min and the resultant mixture was stirred at that temperature for 1 h. Then PhSeSePh (1.49 g, 4.77 mmol, 3.0 eq) was dissolved in dry THF (2 mL) and added dropwise rapidly to the mixture. The solution was subsequently stirred 1 h at -78 °C then 1 h at room temperature before being quenched by saturated aqueous NH_4Cl (100 mL). The aqueous phase was extracted with ether (3 x 100 mL) and the organic layers combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified *via* column chromatography (light petroleum/ethyl acetate = 90:10) to afford the desired product **12** as a colourless solid (550.1 mg, 74%) along with unreacted starting material (64.0 mg, 13%). $R_f = 0.64$ [light petroleum/ethyl acetate (80:20)]. mp 159-160 °C. IR (KBr film) υ_{max} 2898, 1678, 1448, 1413, 1247, 839, 737 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 9 H), 1.36 (m, 1 H), 1.40 (m, 1 H), 1.71 (dm, 1 H, *J* = 11.7 Hz), 1.85 (ddd, 1 H, *J* = 13.2, 7.7, 5.9 Hz), 2.35-2.40 (m, 2 H), 2.82 (d, 1 H, *J* = 15.0 Hz), 3.26 (d, 1 H, *J* = 15.0 Hz), 3.73 (s, 3 H), 6.90 (s, 1 H), 7.18-7.09 (m, 2 H), 7.20-7.28 (m, 3 H), 7.76 (dd, 1 H, *J* = 7.7, 1.8 Hz), 7.72-7.80 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -2.7 (**C**H_3), 21.5 (**C**H_2), 32.4 (**C**H_2), 32.8 (**C**H_3), 34.7 (**C**H_2), 43.5 (**C**H_2), 43.7 (**C**), 70.9 (**C**), 108.4 (**C**H), 113.2 (**C**), 118.2 (**C**H), 121.7 (**C**H), 126.6 (**C**), 126.9 (**C**H), 128.1 (**C**H), 128.5 (2 x **C**H), 129.7 (**C**), 134.4 (**C**), 136.9 (**C**), 138.0 (2 x **C**H), 213.3 (**C**). HRMS (ESI) *m/z* 490.1085 $[M+Na]^+$, $[C_{25}H_{29}NOSiSeNa]^+$ requires 490.1081.



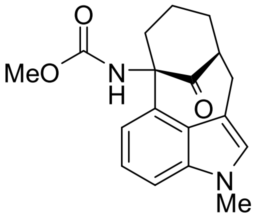
Curtius rearrangement product 15 (Scheme 2). To a stirred solution of the substrate **11** (692 mg, 1.87 mmol) in dry THF (42 mL) under argon was added TBAF

(1 M solution in THF, 2.25 mL, 2.25 mmol, 1.2 eq). The resulting mixture was stirred for 2 h at room temperature then quenched with saturated aqueous NH_4Cl solution (25 mL) and extracted with diethyl ether (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified through a short plug of silica gel (light petroleum/ethyl acetate = 80:20) to give the desired desilylated product as a colourless solid (483 mg, 87%). R_f 0.21 [iso-hexane/ethyl acetate (90:10)]. mp 148-150 °C. Found C, 72.39; H, 6.65; N, 4.65; $C_{18}H_{19}NO_3$ requires C, 72.71; H, 6.44; N, 4.71. IR υ_{max} 2926, 1732, 1701, 1456, 1319, 1060 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (ddm, 1 H, *J* = 14.3, 13.2 Hz), 1.43 (m, 1 H), 1.92 (dm, 1 H, *J* = 13.8 Hz), 2.14 (m, 1 H), 2.20 (dm, 1 H, *J* = 13.5 Hz), 2.66 (ddd, 1 H, *J* = 13.4, 9.5, 3.8 Hz), 3.02 (dd, 1 H, *J* = 15.3, 3.2 Hz), 3.13-3.18 (dm, 1 H, *J* = 15.3 Hz), overlapping 3.18-3.22 (m, 1 H), 3.76 (s, 3 H), 3.85 (s, 3 H), 6.72 (dd, 1 H, *J* = 5.2, 3.1 Hz), 6.96 (s, 1 H), 7.20-7.22 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1 (**C**H_2), 30.3 (**C**H_2), 31.4 (**C**H_2), 32.8 (**C**H_3), 40.4 (**C**H_2), 48.3 (**C**H), 52.4 (**C**H_3), 70.3 (**C**), 107.9 (**C**H), 111.0 (**C**), 118.1 (**C**H), 121.7 (**C**H), 127.4 (2 x **C**), 131.5 (**C**), 137.0 (**C**), 173.6 (**C**), 210.9 (**C**). HRMS (ESI) *m/z* 298.1438 $[M+H]^+$, $[C_{18}H_{20}NO_3]^+$ requires 298.1443.

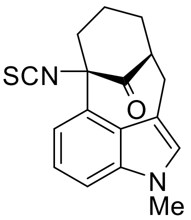
The desilylated substrate (606 mg, 2.25 mmol) was then dissolved in dry pyridine (25 mL), to which was then added freshly dried LiI (3.01 g, 22.5 mmol, 10.0 eq). The flask was then fitted with a condenser under argon and the mixture heated to reflux for 24 h. The crude reaction was quenched with HCl 1 M (500 mL) and extracted with CH_2Cl_2. The combined organic layers were washed three times with H_2O (1 L) then brine (500 mL) then dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the corresponding carboxylic acid as a pale brown solid (505 mg, 88%) used in the next step without further purification. R_f = 0.22 [ethyl acetate/light petroleum (60:40)]. mp 209-214 °C. IR (KBr film) υ_{max} 2938, 1711, 1695, 1452, 1411, 1283, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.41-1.53 (m, 2 H), 1.98 (m, 1 H), 2.17 (m, 1 H), 2.41-2.46 (m, 2 H), 3.07 (dd, 1 H, *J* = 14.7, 2.2 Hz), 3.22-3.34 (m, 2 H), 3.76 (s, 3 H), 6.98 (br. s, 1 H), 7.10 (dd, 1 H, *J* = 7.0, 1.5 Hz), 7.20-7.29 (m, 2 H), ~11.00 (very br. s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8 (**C**H_2), 31.3 (**C**H_2), 31.8 (**C**H_2), 32.8 (**C**H_3), 39.3 (**C**H_2), 47.6 (**C**H), 66.5 (**C**), 109.1 (**C**H), 110.7 (**C**), 117.0 (**C**H), 122.0 (**C**H), 126.6 (**C**), 127.4 (**C**H), 130.2 (**C**), 137.2 (**C**), 172.2 (**C**), 216.5 (**C**). HRMS (ESI) *m/z* 306.1097 $[M+Na]^+$, $[C_{17}H_{17}NO_3Na]^+$ requires 306.1101.

The carboxylic acid (100 mg, 0.35 mmol) was dissolved in dry CH_2Cl_2 (10 mL). Diphenyldiphosphoryl azide (152 µL, 0.71 mmol, 2.0 eq) was added dropwise whilst stirring then NEt_3 (103 µL, 0.74 mmol, 2.1 eq) was syringed in and the resulting mixture heated to reflux for 4 h. The solvent was then removed through a flow of argon. Dry toluene (10 mL) was added and the mixture heated at 90 °C for 24 h. The reaction was subsequently quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified *via* column chromatography (light petroleum/ethyl acetate = 60:40) to afford the desired product **13** (71.3 mg, 63%) as a colourless solid. R_f = 0.23 [light petroleum/ethyl acetate (80:20)]. mp 191-195 °C. IR (KBr film) υ_{max} 3201, 3134, 2940, 2108, 1760, 1457, 1327, 1231, 921, 740 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 (m, 1 H), 1.46 (m, 1 H), 1.94-2.01 (m, 2 H), 2.05-2.13 (m, 2 H), 3.04-3.09 (m, 2 H), 3.45 (dd, 1 H, *J* = 16.8, 7.3 Hz), 3.76 (s, 3 H), 6.62 (br s., 1 H), 6.86 (m, 1 H), 6.93-6.94 (m, 2 H), 7.25 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4 (**C**H_2), 28.6

(**C**H_2), 30.4 (**C**H_2), 32.9 (**C**H_3), 36.1 (**C**H), 45.0 (**C**H_2), 67.8 (**C**), 100.8 (**C**), 109.2 (**C**H), 113.0 (**C**), 114.5 (**C**H), 122.1 (**C**H), 124.9 (**C**), 127.3 (**C**H), 130.2 (**C**), 136.9 (**C**), 158.0 (**C**). HRMS (ESI) *m/z* 346.1274 $[M+Na]^+$, $[C_{17}H_{17}N_5O_2Na]^+$ requires 346.1274; 296.1393 $[M–N_2+H]^+$, $[C_{17}H_{18}N_3O_2]^+$ requires 296.1399; 318.1208 $[M–N_2+Na]^+$, $[C_{17}H_{17}N_3O_2Na]^+$ requires 318.1218.



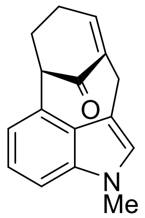
Carbamate 14 (Scheme 2). An oven-dried round-bottom flask, purged with argon, was charged with the substrate **13** (117 mg, 0.36 mmol) in dry MeOH (13 mL). A 30% wt solution of NaOMe in MeOH (72 μL, 0.38 mmol, 1.05 eq) was added dropwise and the resulting solution stirred at room temperature for 3 h. The mixture was subsequently quenched with H_2O (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified *via* column chromatography (light petroleum/ethyl acetate = 80:20) to afford the desired carbamate **14** as a colourless solid (98.4 mg, 87%). R_f = 0.30 [light petroleum/ethyl acetate (80:20)]. mp 82-83 °C. Found C, 69.39; H, 6.47; N, 8.72; $C_{18}H_{20}N_2O_3$ requires C, 69.21; H, 6.45; N, 8.97. IR (KBr film) υ_{max} 3372, 2920, 1736, 1707, 1507, 1490, 1449, 1238, 1052 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.39-1.51 (m, 2 H), 1.91 (dm, *J* 14.0, 1 H), 2.18-2.26 (m, 2 H), 2.90-3.03 (m, 2 H), 3.17-3.29 (m, 2 H), 3.73 (s, 3 H), 3.75 (s, 3 H), 5.77 (br. s, 1 H), 6.95 (br. s, 1 H), 7.25-7.26 (m, 2 H), 7.31 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4 (**C**H_2), 30.8 (**C**H_2), 31.5 (**C**H_2), 32.7 (**C**H_3), 41.3 (**C**H_2), 47.0 (**C**H), 52.0 (**C**H_3), 71.2 (**C**), 108.8 (**C**H), 111.6 (**C**), 115.1 (**C**H), 121.9 (**C**H), 125.7 (**C**), 127.2 (**C**H), 134.2 (**C**), 136.8 (**C**), 156.9 (**C**), 210.9 (**C**). HRMS (ESI) *m/z* 335.1358 $[M+Na]^+$, $[C_{18}H_{20}N_2O_3Na]^+$ requires 335.1366.



Isothiocyanate 15 (Scheme 2). An oven-dried round-bottom flask, purged with argon, was charged with the substrate **14** (82.5 mg, 0.26 mmol) in dry CH_2Cl_2 (10 mL). Trimethylsilyl iodide (72 μL, 0.53 mmol, 2.0 eq) was added while stirring and the mixture heated to reflux for 1.5 h. The solvent was then evaporated through a flow of argon. Dry MeOH (18 mL) was subsequently added under argon and the resulting mixture heated to reflux for 19 h. The solution was cooled down to room temperature and the solvent evaporated under reduced pressure. The crude mixture was columned through a short plug of silica gel (ethyl acetate/methanol = 95:5) to afford the desired amine as a fine brown powder (60.0 mg, 90%). R_f = 0.33 [ethyl acetate/MeOH (90:10)]. mp 88-89 °C. IR (KBr film) υ_{max} 3422, 2923, 1710, 1449, 1418, 1316, 780, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.39-1.53 (m, 2 H), 1.83

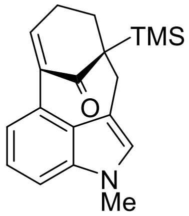
(m, 1 H), 2.21 (m, 1 H), 2.38-2.50 (m, 2 H overlapping), 3.02 (dd, 1 H, *J* = 16.2, 3.3 Hz), 3.12 (dd, 1 H, *J* = 16.2, 5.5 Hz), 3.29 (m, 1 H), 3.76 (s, 3 H), 5.42 (br. s, 2 H), 6.97 (s, 1 H), 7.26-7.34 (m, 2 H), 7.70 (dd, 1 H, *J* = 7.0, 1.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2 (**C**H_2), 30.4 (**C**H_2), 31.7 (**C**H_2), 32.9 (**C**H_3), 43.2 (**C**H_2), 46.9 (**C**H), 70.5 (**C**), 109.5 (**C**H), 111.0 (**C**), 116.0 (**C**H), 122.2 (**C**H), 125.6 (**C**), 127.5 (**C**H), 131.4 (**C**), 136.8 (**C**), 213.4 (**C**). HRMS (ESI) *m/z* 255.1492 $[M+H]^+$, $[C_{17}H_{18}N_2O]^+$ requires 255.1497.

An oven-dried round-bottom flask, purged with argon, was charged with the amine (28.2 mg, 0.11 mmol), DMAP (1.6 mg, 0.01 mmol, 0.09 eq) in dry dichloroethane (2 mL). 1,1'-thiocarbonyldi-2-(1H)-pyridone (34.2 mg, 0.15 mmol, 1.3 eq) was added and the reaction mixture heated at 70 °C for 15 h. The solvent was subsequently concentrated under reduced pressure and the residue purified on silica gel (ethyl acetate/light petroleum = 90:10) to afford the desired compound **15** (25.0 mg, 76%). R_f = 0.75 [ethyl acetate/MeOH (99:1)]. mp 198-199 °C. IR (KBr film) υ_{max} 2923, 2851, 2120 (-N=C=S), 1713, 1457, 1315, 741 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (m, 1 H), 1.50 (m, 1 H), 2.00 (d, 1 H, *J* = 14.1 Hz), 2.17 (m, 1 H), 2.42-2.48 (m, 2 H), 3.07 (dd, 1 H, *J* = 15.4, 3.0 Hz), 3.26 (dd, 1 H, *J* = 15.3, 5.5 Hz), 3.30 (m, 1 H), 3.77 (s, 3 H), 6.98 (s, 1 H), 7.10 (d, 1 H, *J* = 7.2 Hz), 7.23 (dd, 1 H, *J* = 8.1, 7.7 Hz), 7.26 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.0 (**C**H_2), 30.4 (**C**H_2), 31.9 (**C**H_2), 32.8 (**C**H_3), 45.5 (**C**H_2), 47.1 (**C**H), 78.9 (**C**), 109.3 (**C**H), 110.8 (**C**), 116.2 (**C**H), 122.0 (**C**H), 125.0 (**C**), 127.5 (**C**H), 130.5 (**C**), 136.9 (**C**), 137.9 (**C**), 205.9 (**C**). HRMS (EI) *m/z* 296.0972 $[M]^+$, $[C_{17}H_{16}N_2OS]^+$ requires 296.0983.

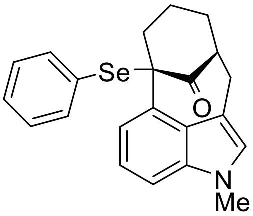


Bridgehead alkene 16 (Scheme 3). An oven-dried round-bottom flask, purged with argon, was charged with the substrate **10** (20.0 mg, 0.051 mmol) in dry CH_2Cl_2 (2 mL) and cooled down to -10 °C. *m*CPBA (12.5 mg, 0.072 mmol, 1.0 eq) was added in one pot and the resulting solution stirred at that maintained temperature for 15 min. The reaction was quenched with water (5 mL) washed with Na_2SO_3 (5 mL) then brine (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were subsequently treated with saturated aqueous NH_4Cl (5 mL), brine (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified *via* column chromatography (light petroleum/ethyl acetate = 80:20) to give the desired product **16** as a colourless solid (8.3 mg, 69%). R_f = 0.48 [light petroleum/ethyl acetate (80:20)]. mp 110-112 °C. IR (KBr film) υ_{max} 2853, 1709, 1444, 1417, 1312, 783, 745 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (m, 1 H), 2.18-2.27 (m, 2 H), 2.69 (m, 1 H), 3.55 (d, 1 H, *J* = 14.3 Hz), 3.72 (s, 3 H), 3.90 (dd, 1 H, *J* = 14.0, 1.5 Hz), 4.19 (dd, 1 H, *J* = 8.9, 3.3 Hz), 6.21 (m, 1 H), 6.92 (s, 1 H), 6.95 (t, 1 H, *J* = 4.4 Hz), 7.15-7.16 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8 (**C**H_2), 29.3 (**C**H_2), 30.6 (**C**H_2), 32.8 (**C**H_3), 55.8 (**C**H), 107.9 (**C**H), 112.6 (**C**), 119.0 (**C**H), 121.5 (**C**H), 124.7

(**C**), 125.2 (**C**H), 129.4 (**C**H), 135.0 (**C**), 137.5 (**C**), 141.3 (**C**), 208.5 (**C**). HRMS (ESI) *m/z* 260.1058 $[M+Na]^+$, $[C_{16}H_{15}NONa]^+$ requires 260.1051.

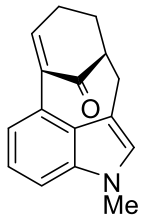


Bridgehead alkene 18 (Scheme 3). An oven-dried round-bottom flask, purged with argon, was charged with the substrate **12** (20.0 mg, 0.043 mmol) in dry CH_2Cl_2 (2 mL) and cooled down to -10 °C. *m*CPBA (7.4 mg, 0.043 mmol, 1.0 eq) was added in one pot and the resulting solution stirred at that maintained temperature for 15 min. The reaction was quenched with water (5 mL) washed with Na_2SO_3 (5 mL) then brine (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were subsequently treated with saturated aqueous NH_4Cl (5 mL), brine (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified *via* column chromatography (light petroleum/ethyl acetate = 95:5) to give the desired product **18** as a colourless solid (6.6 mg, 50%). R_f = 0.82 [light petroleum/ethyl acetate (90:10)]. mp 222-223 °C. IR (KBr film) υ_{max} 2945, 2845, 1686, 1452, 1305, 1246, 857, 837, 748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.13 (s, 9 H), 1.91 (m, 1 H), 2.13-2.31 (m, 2 H), 2.43 (m, 1 H), 2.74 (dm, 1 H, *J* = 15.1 Hz), 3.17 (d, 1 H, *J* = 15.1 Hz), 3.69 (s, 3 H), 6.31 (dd, 1 H, *J* = 7.0, 3.7 Hz), 6.75 (dd, 1 H, *J* = 1.5 Hz), 7.02 (dd, 1 H, *J* = 6.7, 1.1 Hz), 7.12-7.21 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -2.6 (**C**H_3), 21.1 (**C**H_2), 31.6 (**C**H_2), 32.6 (**C**H_3), 34.6 (**C**H_2), 44.3 (**C**), 108.3 (**C**H), 114.2 (**C**H), 114.4 (**C**), 122.5 (**C**H), 126.1 (**C**H), 127.6 (**C**H), 127.9 (**C**), 131.5 (**C**), 135.8 (**C**), 143.4 (**C**), 208.9 (**C**). HRMS (ESI) *m/z* 332.1436 $[M+Na]^+$, $[C_{19}H_{23}NOSiNa]^+$ requires 332.1447.

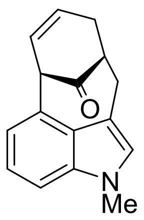


Desilylated compound 17 (Scheme 3). A solution of TBAT (270 mg, 0.50 mmol, 1.1 eq) in dry THF (10 mL) was added dropwise to a solution of substrate **12** (212.7 mg, 0.46 mmol) in dry THF (10 mL) under argon. The solution was then stirred at room temperature for 4.5 h before being quenched with saturated aqueous NH_4Cl (20 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified *via* column chromatography (light petroleum/ethyl acetate = 80:20) to afford the desired product **17** as a colourless solid (101.7 mg, 57%). R_f = 0.40 [light petroleum/ethyl acetate (80:20)]. mp 54-57 °C. IR (KBr film) υ_{max} 2920, 1699, 1446, 1415, 1313, 739, 691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.36-1.55 (m, 2 H), 1.92

(m, 1 H), 2.02 (m, 1 H), 2.34-2.48 (m, 2 H), 2.99 (d, 1 H, *J* = 13.3 Hz), 3.20-3.33 (m, 2 H), 3.76 (s, 3 H), 6.95 (s, 1 H), 7.23-7.25 (m, 2 H), 7.27-7.32 (m, 3 H), 7.74-7.77 (m, 2 H), 7.86 (dd, 1 H, *J* = 5.5, 2.9 Hz). ^{13}C NMR (75 MHz, CDCl$_3$) δ 20.7 (**C**H$_2$), 31.3 (**C**H$_2$), 31.5 (**C**H$_2$), 32.6 (**C**H$_3$), 44.4 (**C**H$_2$), 47.6 (**C**H), 70.8 (**C**), 108.4 (**C**H), 111.4 (**C**), 118.5 (**C**H), 121.6 (**C**H), 126.2 (**C**), 127.0 (**C**H), 127.8 (**C**H), 128.4 (**C**H), 130.0 (**C**), 133.2 (**C**), 136.8 (**C**H), 137.9 (**C**), 210.4 (**C**). HRMS (ESI) *m/z* 418.0689 [M+Na]$^+$, [C$_{22}$H$_{21}$NOSeNa]$^+$ requires 418.0686.

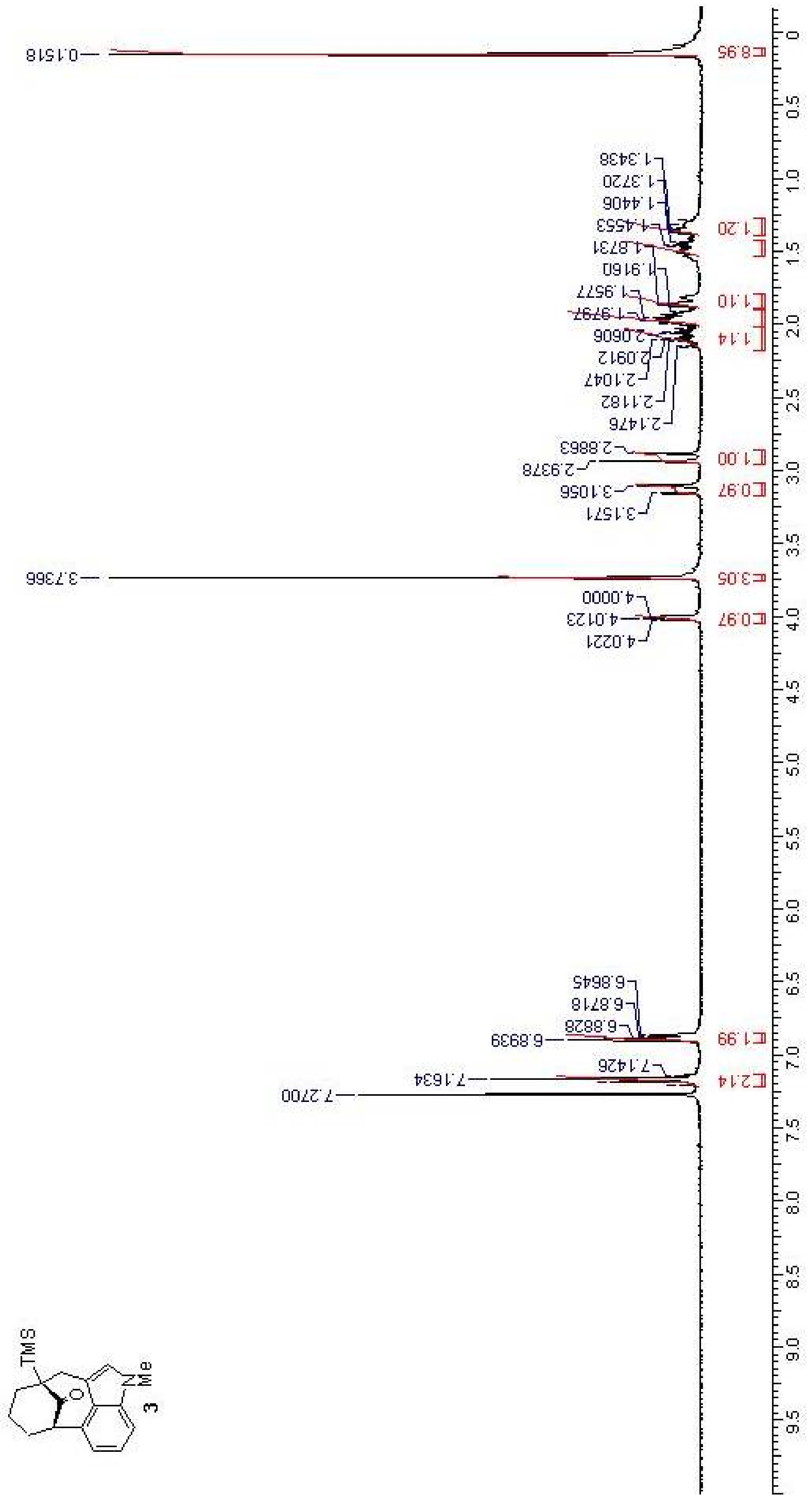


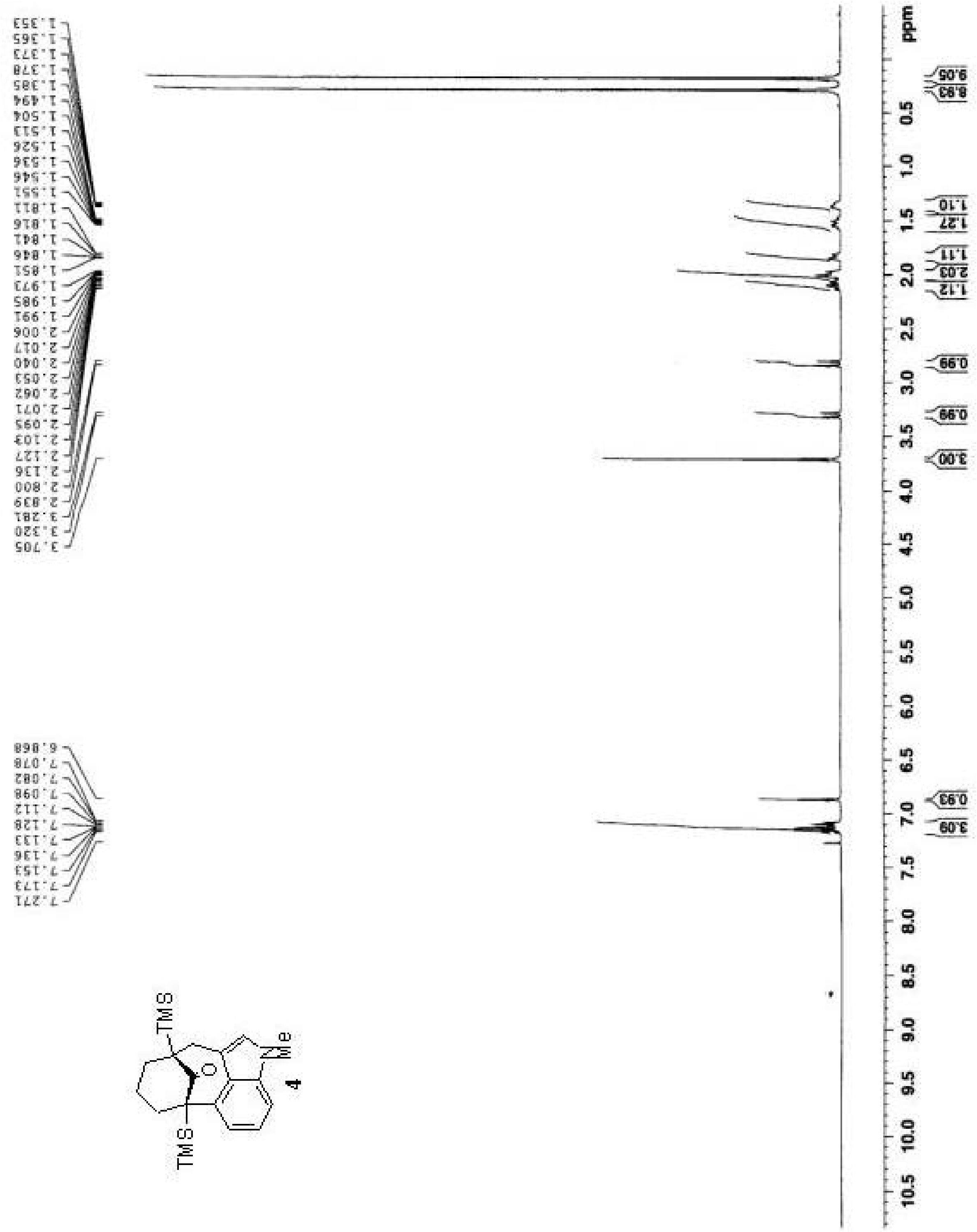
Bridgehead alkene 19 (Scheme 3). An oven-dried round-bottom flask, purged with argon, was charged with the substrate **17** (20.0 mg, 0.051 mmol) in dry CH$_2$Cl$_2$ (2 mL) and cooled down to -10 °C. *m*CPBA (12.5 mg, 0.072 mmol, 1.0 eq) was added in one pot and the resulting solution stirred at that maintained temperature for 15 min. The reaction was quenched with water (5 mL) washed with Na$_2$SO$_3$ (5 mL) then brine (5 mL) and extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were subsequently treated with saturated aqueous NH$_4$Cl (5 mL), brine (5 mL) and extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified *via* column chromatography (light petroleum/ethyl acetate = 80:20) to give the desired product **19** as a colourless solid (7.9 mg, 66%). R$_f$ = 0.36 [light petroleum/ethyl acetate (80:20)]. mp 134-136 °C. IR (KBr film) υ$_{max}$ 2930, 1710, 1448, 1419, 1303, 752 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.99 (m, 1 H), 2.30-2.38 (m, 2 H), 2.44 (m, 1 H), 2.67 (m, 1 H), 3.17-3.25 (m, 2 H), 3.69 (s, 3 H), 6.34 (dd, 1 H, *J* = 7.0, 2.9 Hz), 6.78 (d, 1 H, *J* = 1.1 Hz), 7.05 (d, 1 H, *J* = 7.0 Hz), 7.16 (d, 1 H, *J* = 8.0 Hz), 7.20 (t, 1 H, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.2 (**C**H$_2$), 27.0 (**C**H$_2$), 30.6 (**C**H$_2$), 32.6 (**C**H$_3$), 49.1 (**C**H), 108.5 (**C**H), 113.1 (**C**), 114.3 (**C**H), 122.5 (**C**H), 126.5 (**C**H), 127.7 (**C**), 129.8 (**C**H), 130.9 (**C**), 135.9 (**C**), 142.5 (**C**), 207.4 (**C**). HRMS (ESI) *m/z* 260.1060 [M+Na]$^+$, [C$_{16}$H$_{15}$NONa]$^+$ requires 260.1051.



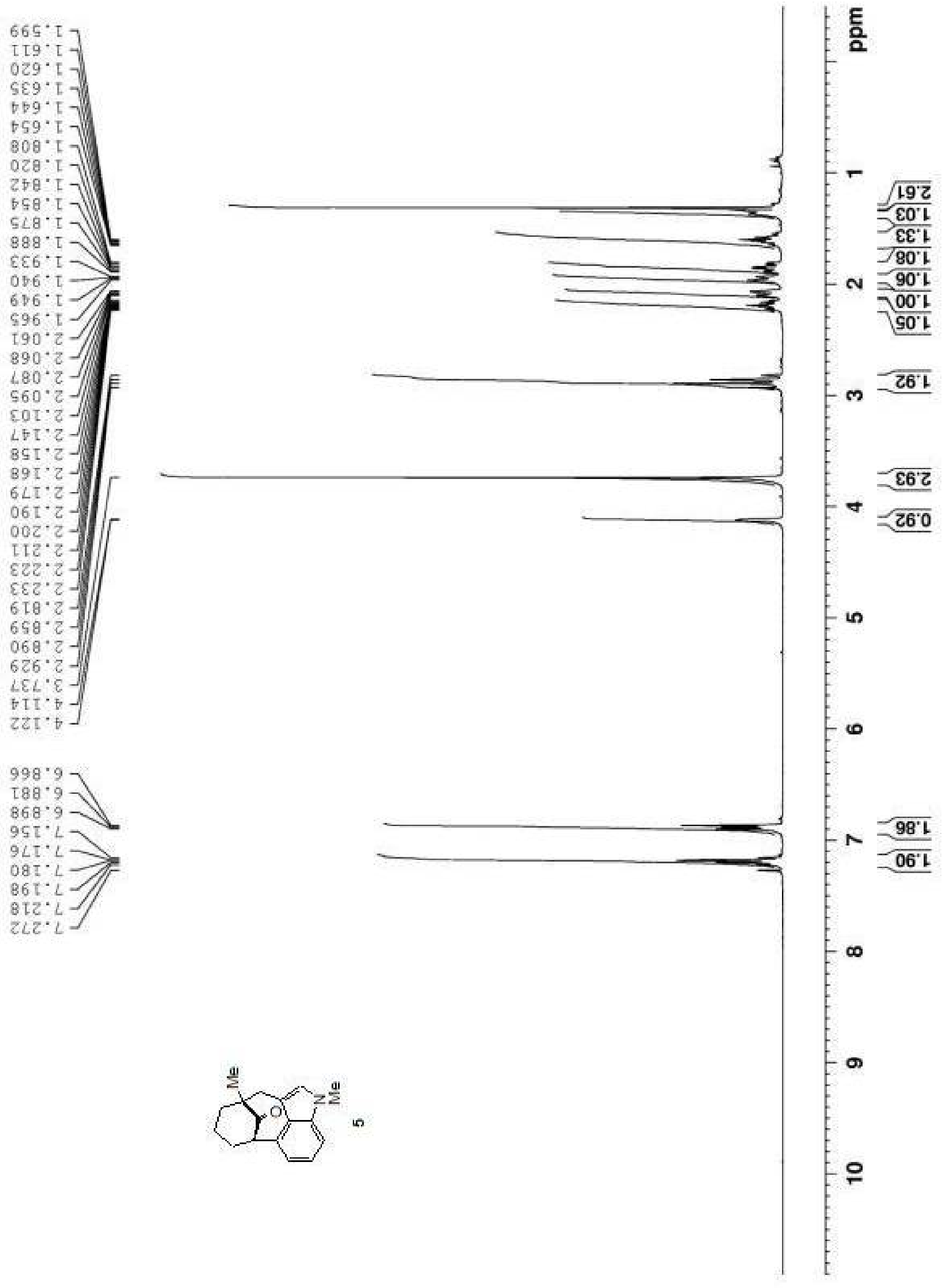
Alkene 20 (Scheme 4). An oven-dried round-bottom flask, purged with argon, was charged with the substrate **16** (25.0 mg, 0.105 mmol) in absolute EtOH (2 mL). RhCl$_3$.xH$_2$O (4.0 mg, 0.016 mmol, 0.06 eq) was added and the resulting solution heated to reflux for 24 h. The reaction was subsequently filtered through celite and concentrated under reduced pressure. The residue was purified *via* column chromatography (light petroleum/ethyl acetate = 90:10) to give the desired product **20** as a colourless solid (13.2 mg, 53%). R$_f$ = 0.56 [light petroleum/ethyl acetate (80:20)]. mp 109-110 °C. IR (KBr film) υ$_{max}$ 2916, 1702, 1458, 1419, 1317, 779, 747 cm^{-1}. ^{1}H

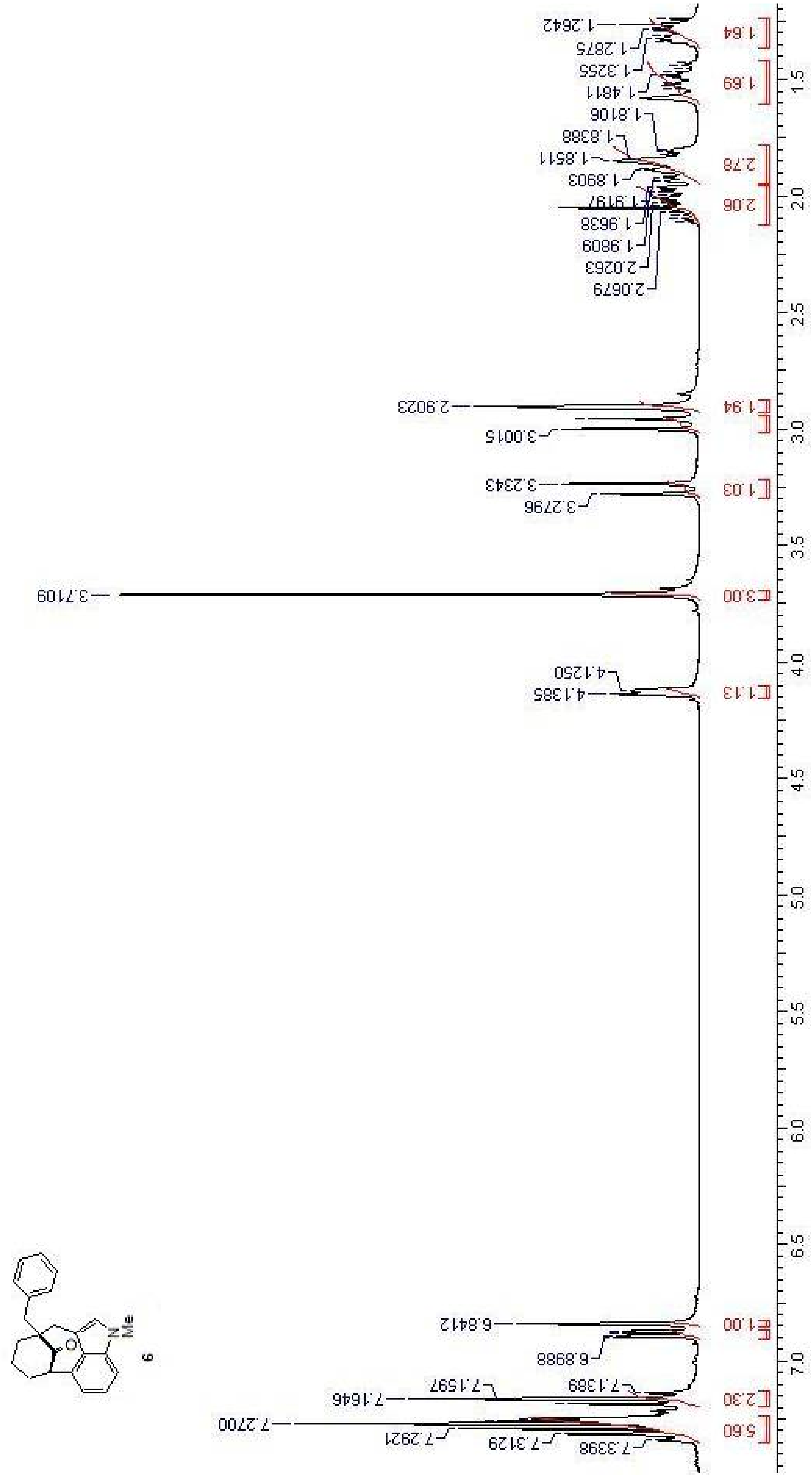
NMR (300 MHz, $CDCl_3$) δ 2.68 (ddd, 1 H, *J* = 12.8, 5.5, 1.4 Hz), 3.01-3.10 (m, 2 H), 3.21 (dd, 1 H, *J* = 15.5, 4.5 Hz), 3.41 (m, 1 H), 3.72 (s, 3 H), 4.20 (d, 1 H, *J* = 5.6 Hz), 5.63-5.75 (m, 2 H), 6.89 (br. s, 1 H), 6.92 (dd, 1 H, *J* = 6.2, 1.8 Hz), 7.15-7.23 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7 (**C**H_2), 32.7 (**C**H_3), 37.9 (**C**H_2), 48.7 (**C**H), 55.8 (**C**H), 107.5 (**C**H), 110.3 (**C**), 118.8 (**C**H), 121.7 (**C**H), 126.0 (**C**), 126.3 (**C**H), 126.5 (**C**H), 129.5 (**C**H), 132.4 (**C**), 137.3 (**C**), 213.8 (**C**). HRMS (ESI) *m/z* 260.1049 $[M+Na]^+$, $[C_{16}H_{15}NONa]^+$ requires 260.1051.

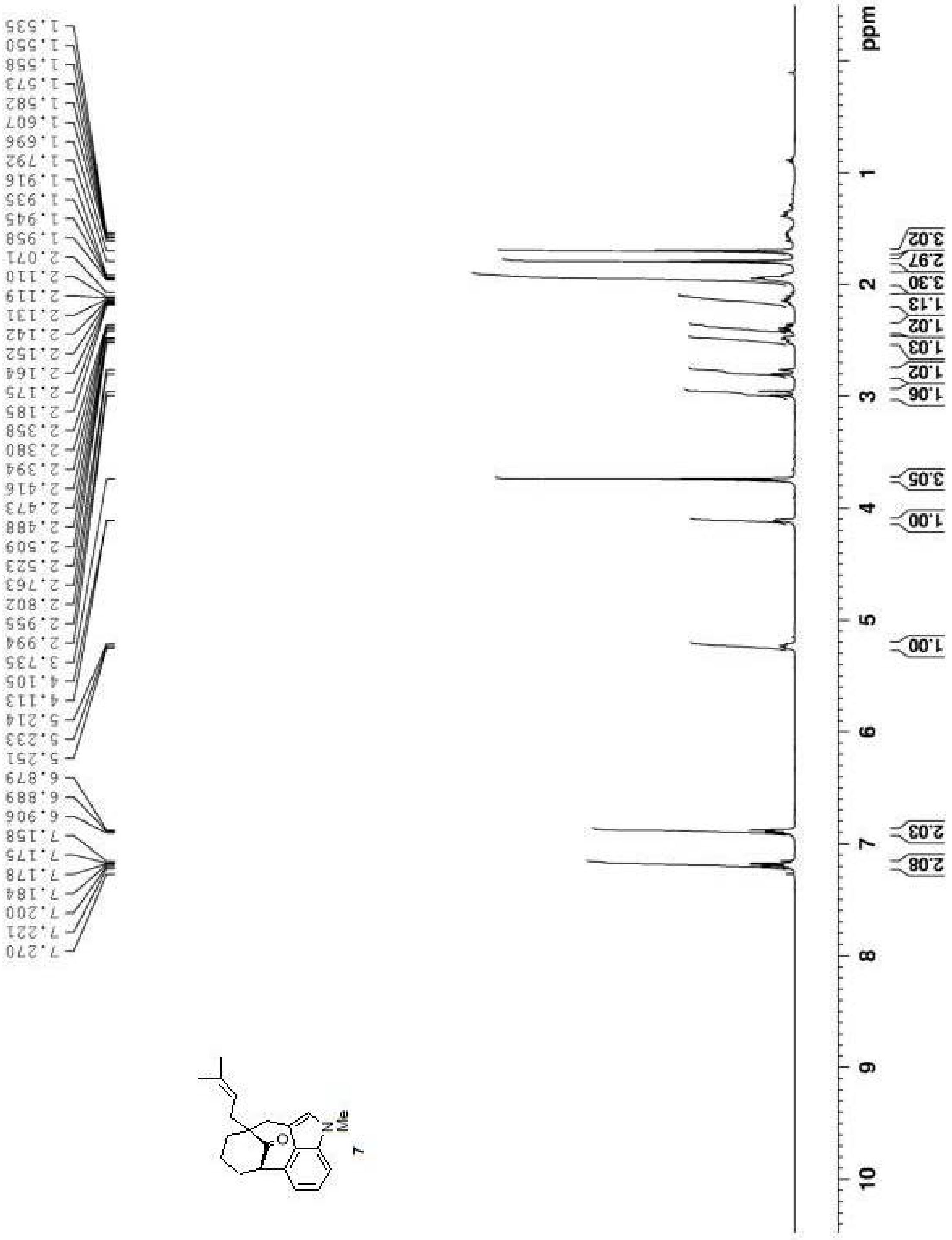

0.1518
1.3438
1.3720
1.4406
1.4553
1.8731
1.9160
1.9577
1.9797
2.0606
2.0912
2.1047
2.1182
2.1476
2.8863
2.9378
3.1056
3.1571
3.7366
4.0000
4.0123
4.0221
6.8645
6.8718
6.8828
6.8939
7.1426
7.1634
7.2700
8.95
1.20
1.10
1.14
1.00
0.97
3.05
0.97
1.99
2.14
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
TMS
O
N
Me
3


1.353
1.365
1.373
1.378
1.385
1.494
1.504
1.513
1.526
1.536
1.546
1.551
1.811
1.816
1.841
1.846
1.851
1.973
1.985
1.991
2.006
2.017
2.040
2.053
2.062
2.071
2.095
2.103
2.127
2.136
2.800
2.839
3.281
3.320
3.705
6.868
7.078
7.082
7.098
7.112
7.128
7.133
7.136
7.153
7.173
7.271
TMS
TMS
O
N
Me
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10.5
9.05
8.93
1.10
1.27
1.11
2.03
1.12
0.99
0.99
3.00
0.93
3.09

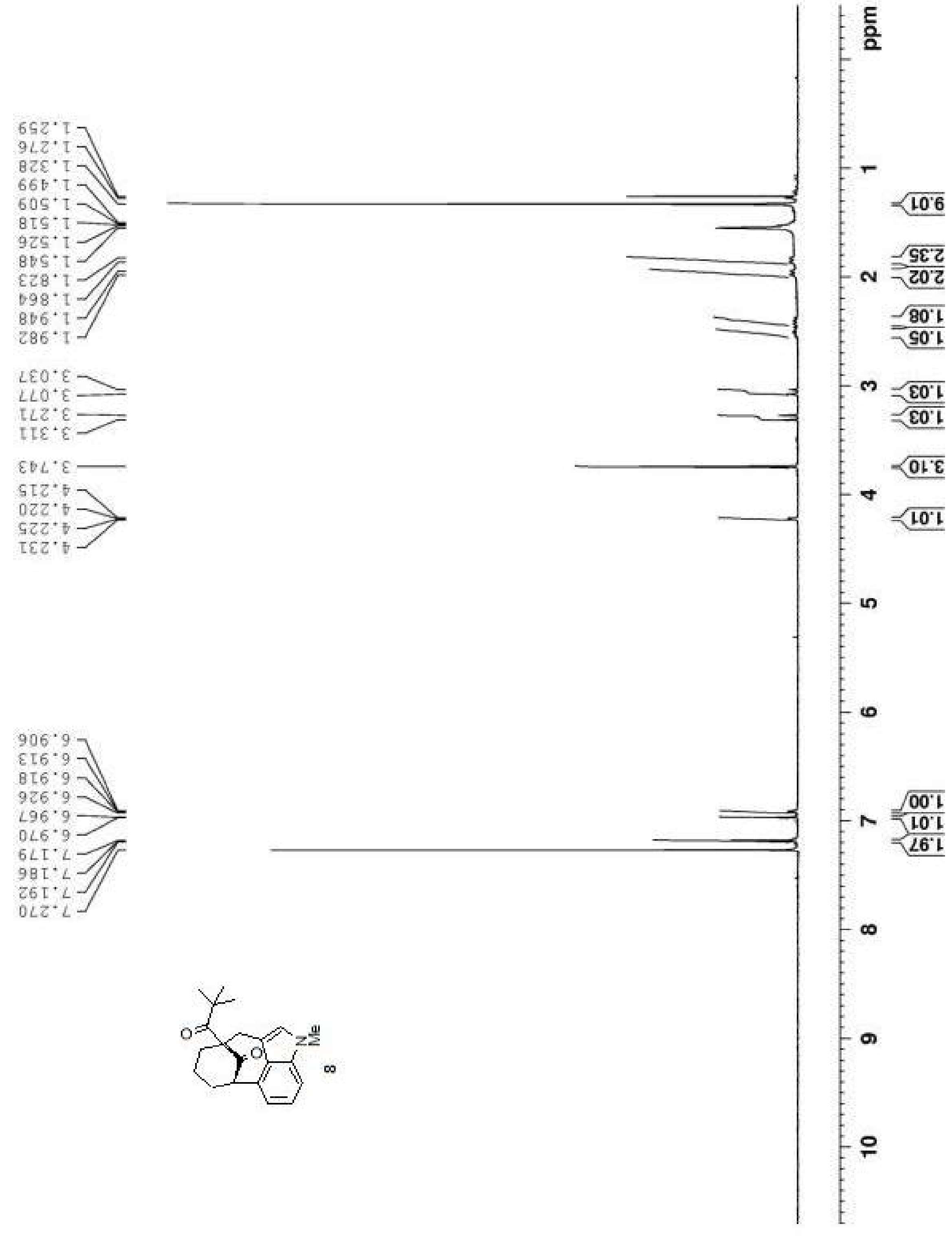
4


1.599
1.611
1.620
1.635
1.644
1.654
1.808
1.820
1.842
1.854
1.875
1.888
1.933
1.940
1.949
1.965
2.061
2.068
2.087
2.095
2.103
2.147
2.158
2.168
2.179
2.190
2.200
2.211
2.223
2.233
2.819
2.859
2.890
2.929
3.737
4.114
4.122
6.866
6.881
6.898
7.156
7.176
7.180
7.198
7.218
7.272
2.61
1.03
1.33
1.08
1.06
1.00
1.05
1.92
2.93
0.92
1.86
1.90
ppm
1
2
3
4
5
6
7
8
9
10
Me
O
N
Me
5

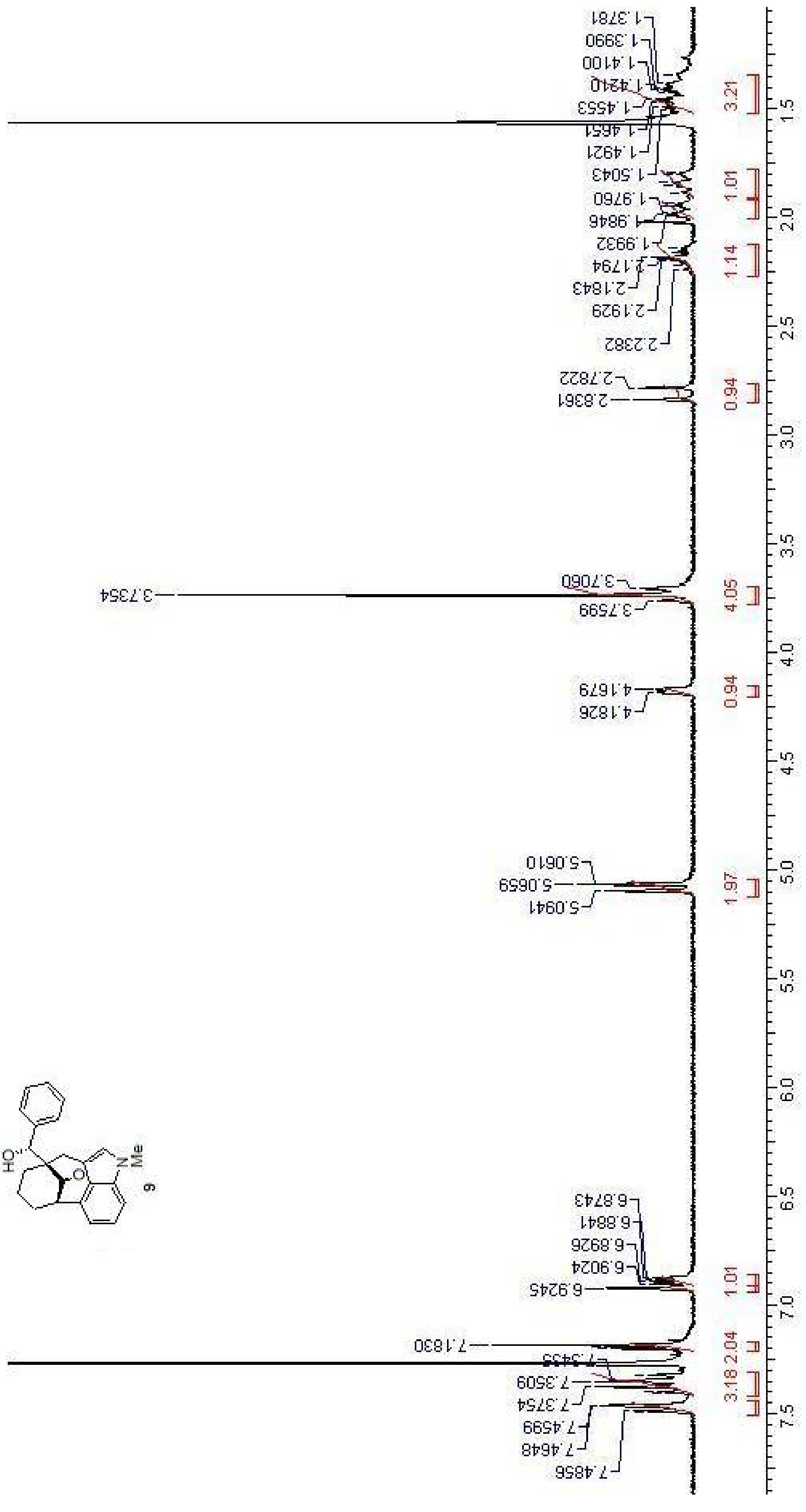

6
Me
N
O
7.3398
7.3129
7.2921
7.2700
7.1646
7.1597
7.1389
6.8988
6.8412
4.1385
4.1250
3.7109
3.2796
3.2343
3.0015
2.9023
2.0679
2.0263
1.9809
1.9638
1.9197
1.8903
1.8511
1.8388
1.8106
1.4811
1.3255
1.2875
1.2642
5.60
2.30
1.00
1.13
3.00
1.03
1.94
2.06
2.78
1.69
1.64
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

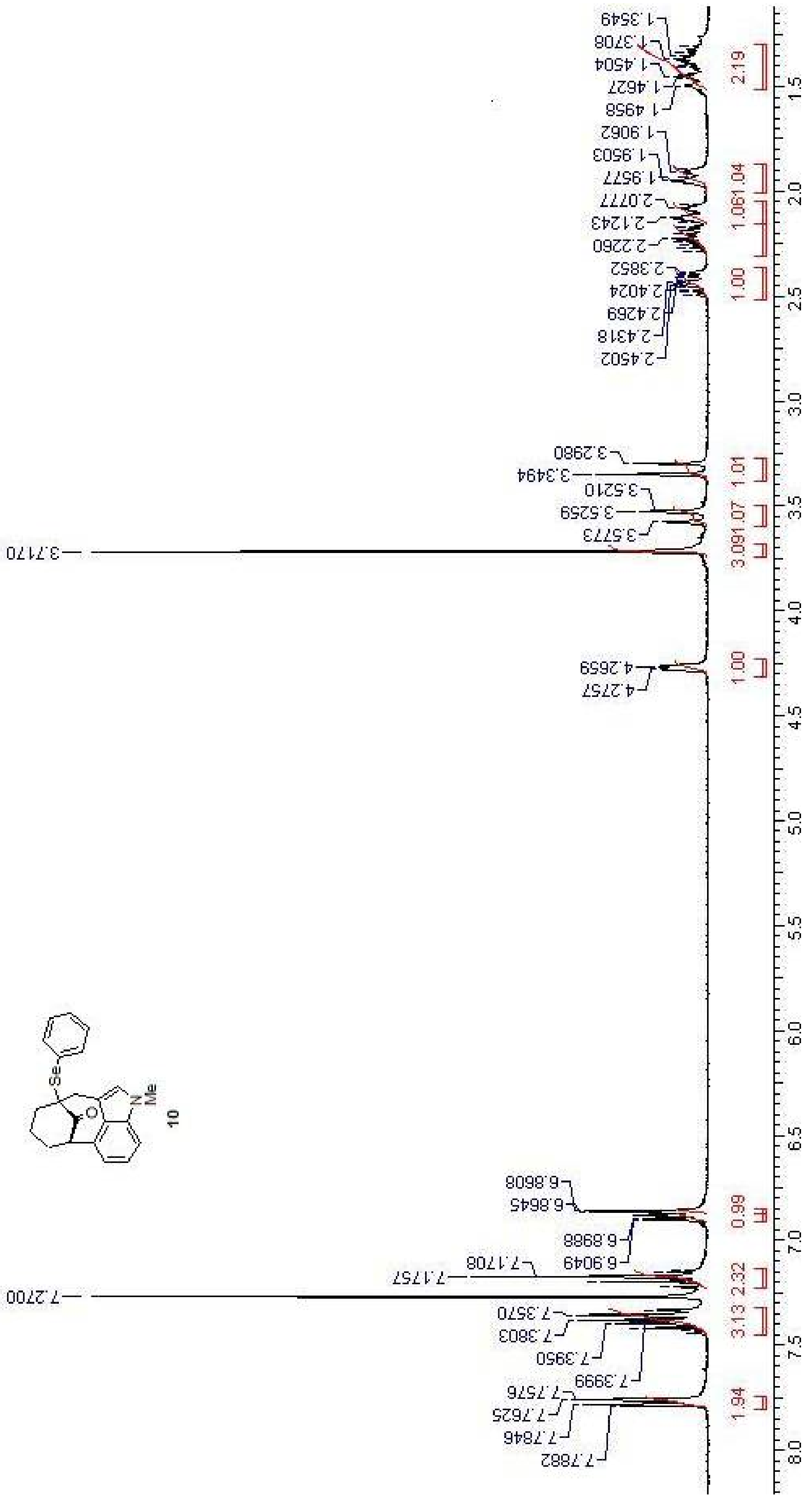

1.535
1.550
1.558
1.573
1.582
1.607
1.696
1.792
1.916
1.935
1.945
1.958
2.071
2.110
2.119
2.131
2.142
2.152
2.164
2.175
2.185
2.358
2.380
2.394
2.416
2.473
2.488
2.509
2.523
2.763
2.802
2.955
2.994
3.735
4.105
4.113
5.214
5.233
5.251
6.879
6.889
6.906
7.158
7.175
7.178
7.184
7.200
7.221
7.270
3.02
2.97
3.30
1.13
1.02
1.03
1.02
1.06
3.05
1.00
1.00
2.03
2.08
ppm
1
2
3
4
5
6
7
8
9
10
O
N
Me

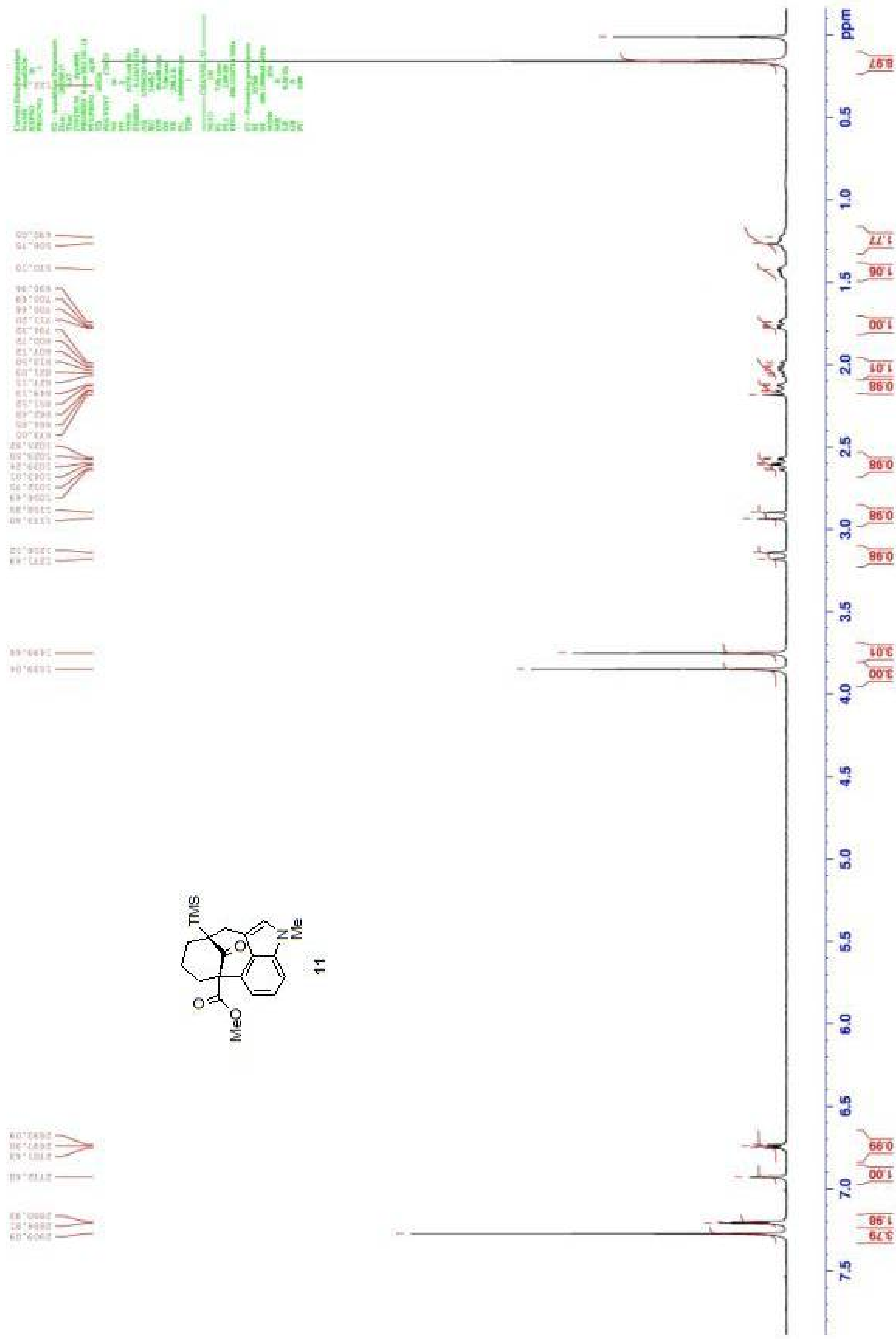
7

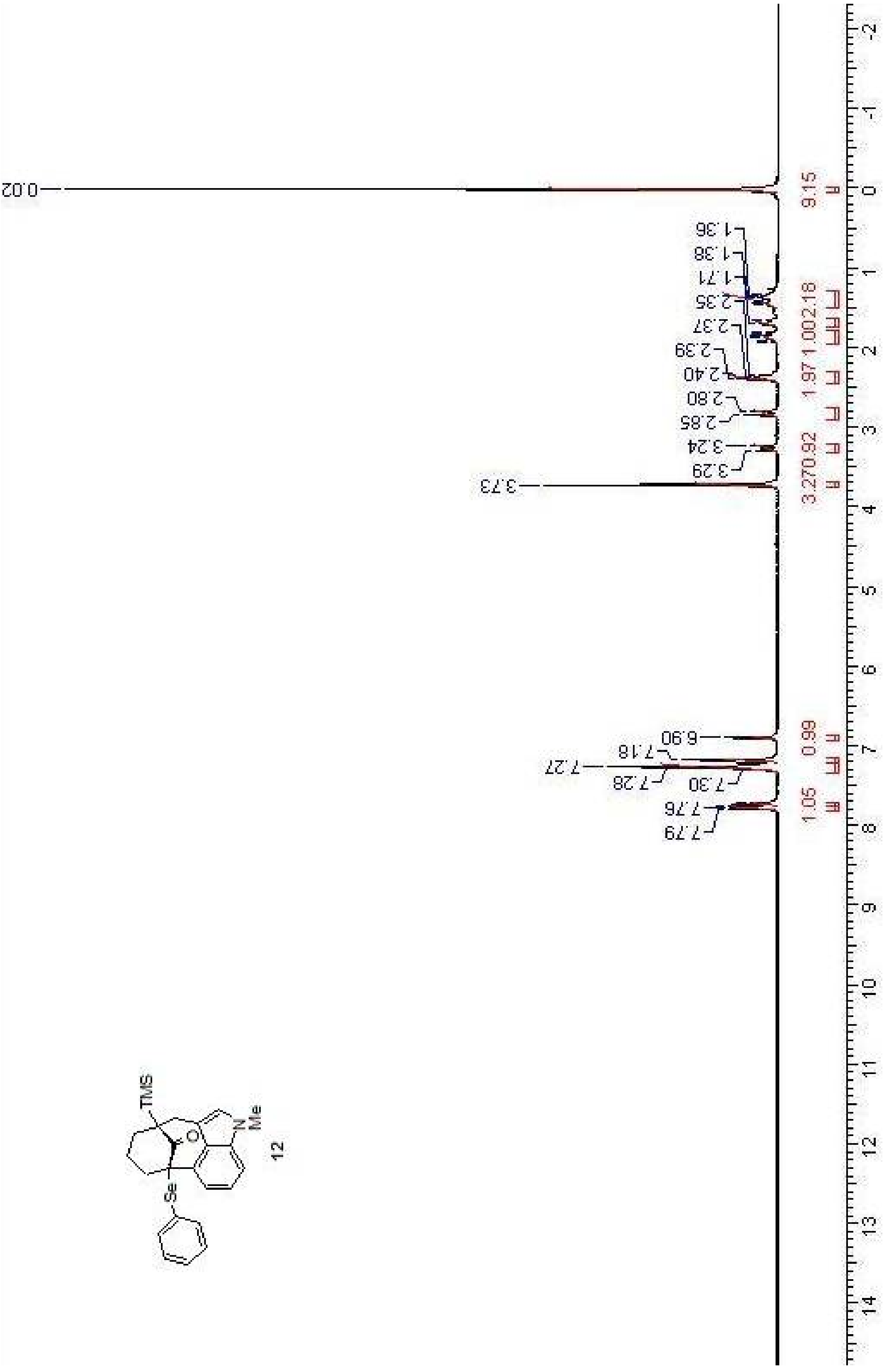

1.259
1.276
1.328
1.499
1.509
1.518
1.526
1.548
1.823
1.864
1.948
1.982
3.037
3.077
3.271
3.311
3.743
4.215
4.220
4.225
4.231
6.906
6.913
6.918
6.926
6.967
6.970
7.179
7.186
7.192
7.270
9.01
2.35
2.02
1.08
1.05
1.03
1.03
3.10
1.01
1.00
1.01
1.97
ppm
1
2
3
4
5
6
7
8
9
10
O
O
N
Me

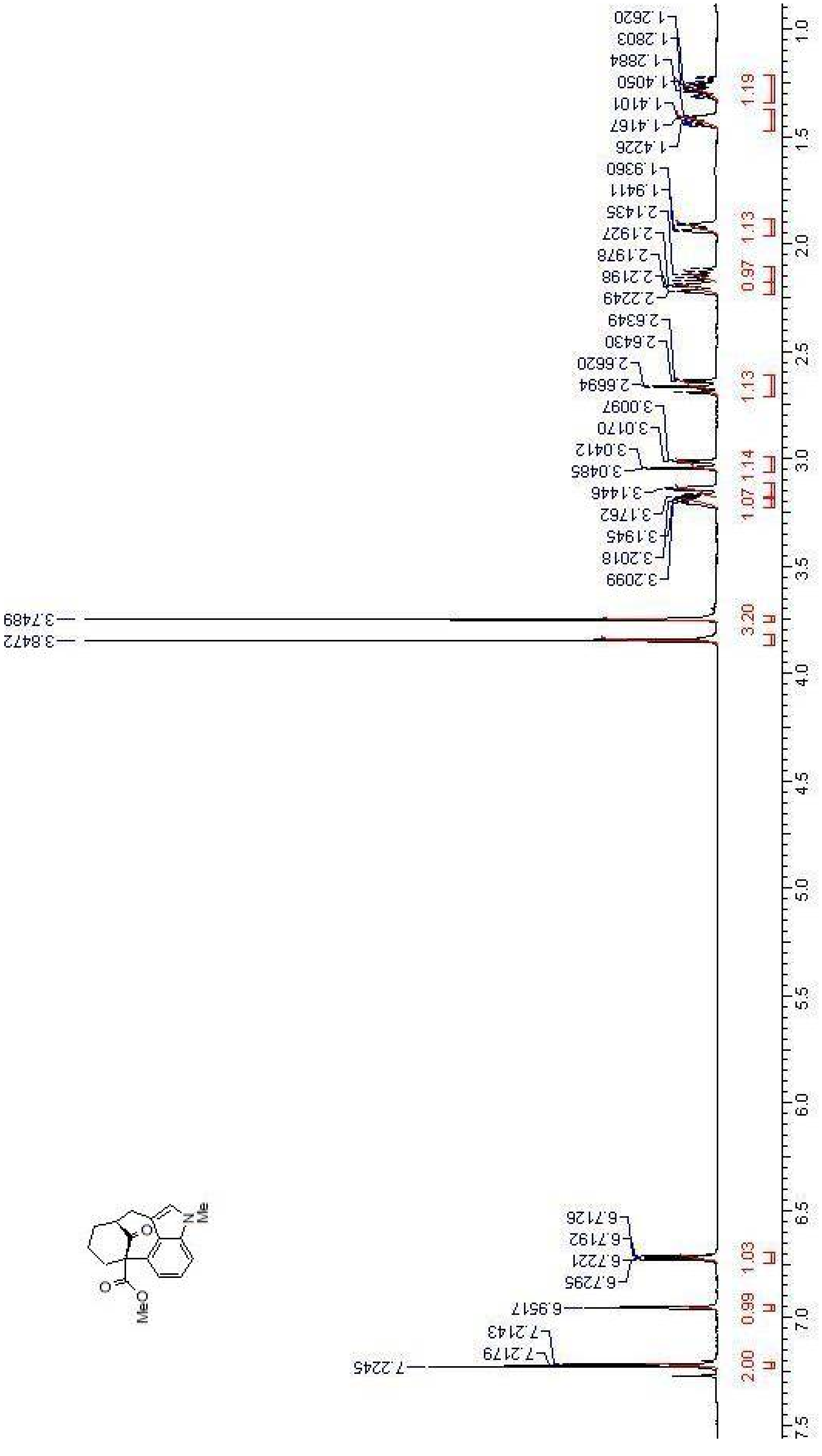
8

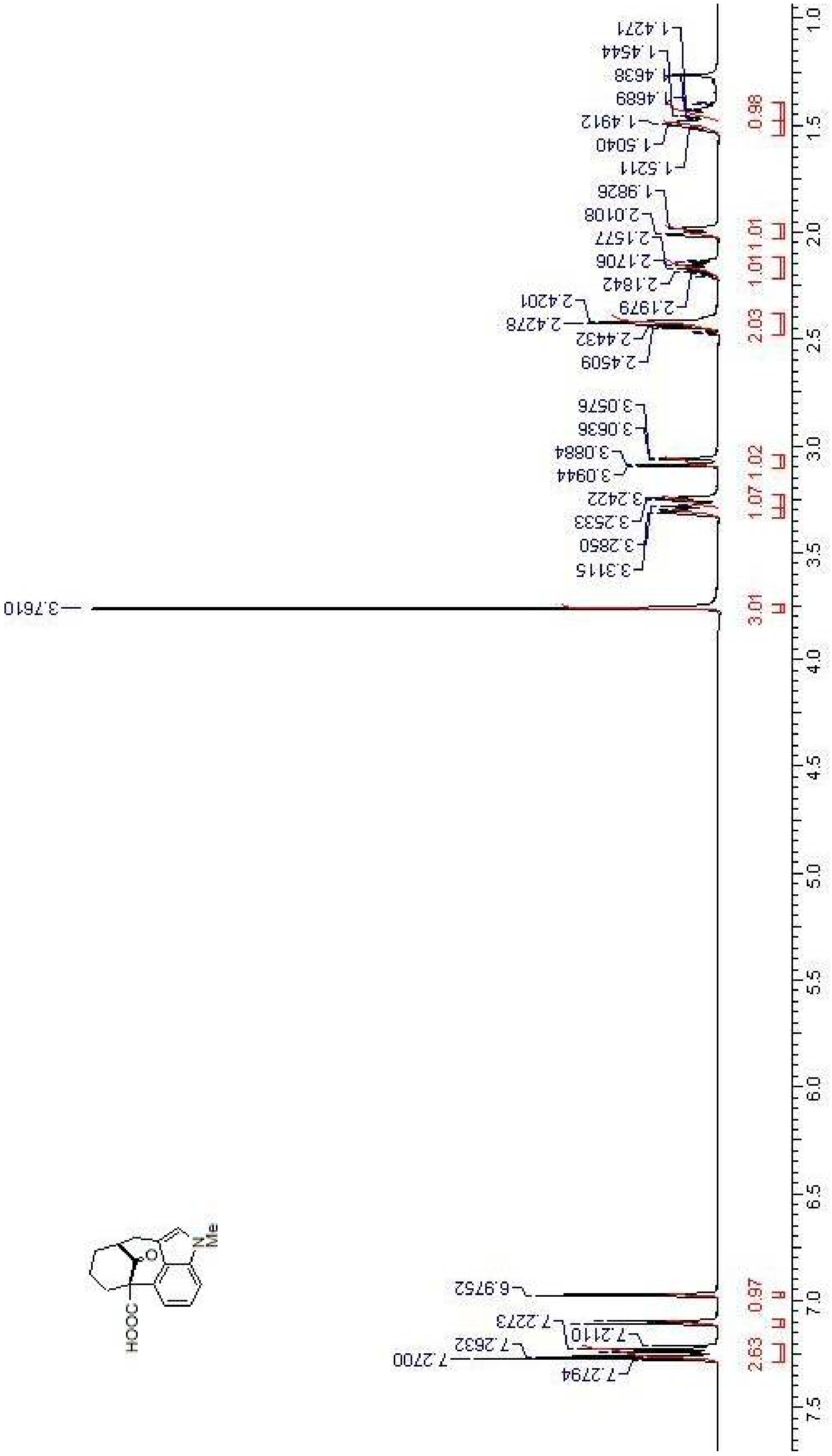

1.3781
1.3990
1.4100
1.4210
1.4553
1.4651
1.4921
1.5043
1.9760
1.9846
1.9932
2.1794
2.1843
2.1929
2.2382
2.7822
2.8361
3.7060
3.7354
3.7599
4.1679
4.1826
5.0610
5.0659
5.0941
6.8743
6.8841
6.8926
6.9024
6.9245
7.1830
7.3435
7.3509
7.3754
7.4599
7.4648
7.4856
3.21
1.01
1.14
0.94
4.05
0.94
1.97
1.01
3.18
2.04
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
HO
O
N
Me
9

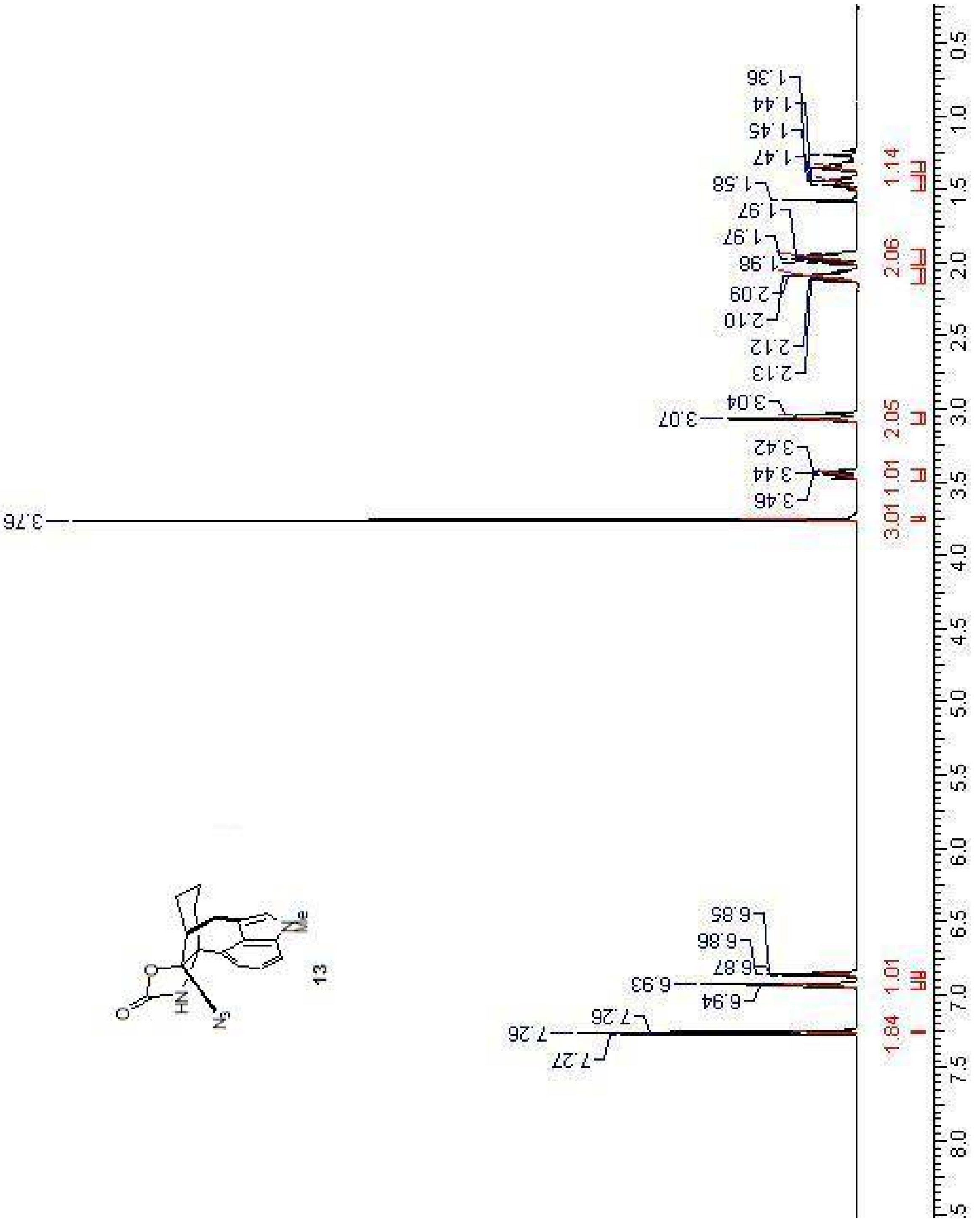

1.3549
1.3708
1.4504
1.4627
1.4958
1.9062
1.9503
1.9577
2.0777
2.1243
2.2260
2.3852
2.4024
2.4269
2.4318
2.4502
3.2980
3.3494
3.5210
3.5259
3.5773
3.7170
4.2659
4.2757
6.8608
6.8645
6.8988
6.9049
7.1708
7.1757
7.2700
7.3570
7.3803
7.3950
7.3999
7.7576
7.7625
7.7846
7.7882
2.19
1.06
1.04
1.00
1.01
3.09
1.07
1.00
0.99
2.32
3.13
1.94
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
Se
O
N
Me
10


ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
6.97
1.77
1.06
1.00
1.01
0.98
0.98
0.98
0.98
3.01
3.00
0.99
1.00
1.98
3.79
TMS
O
N
Me
MeO
O
11

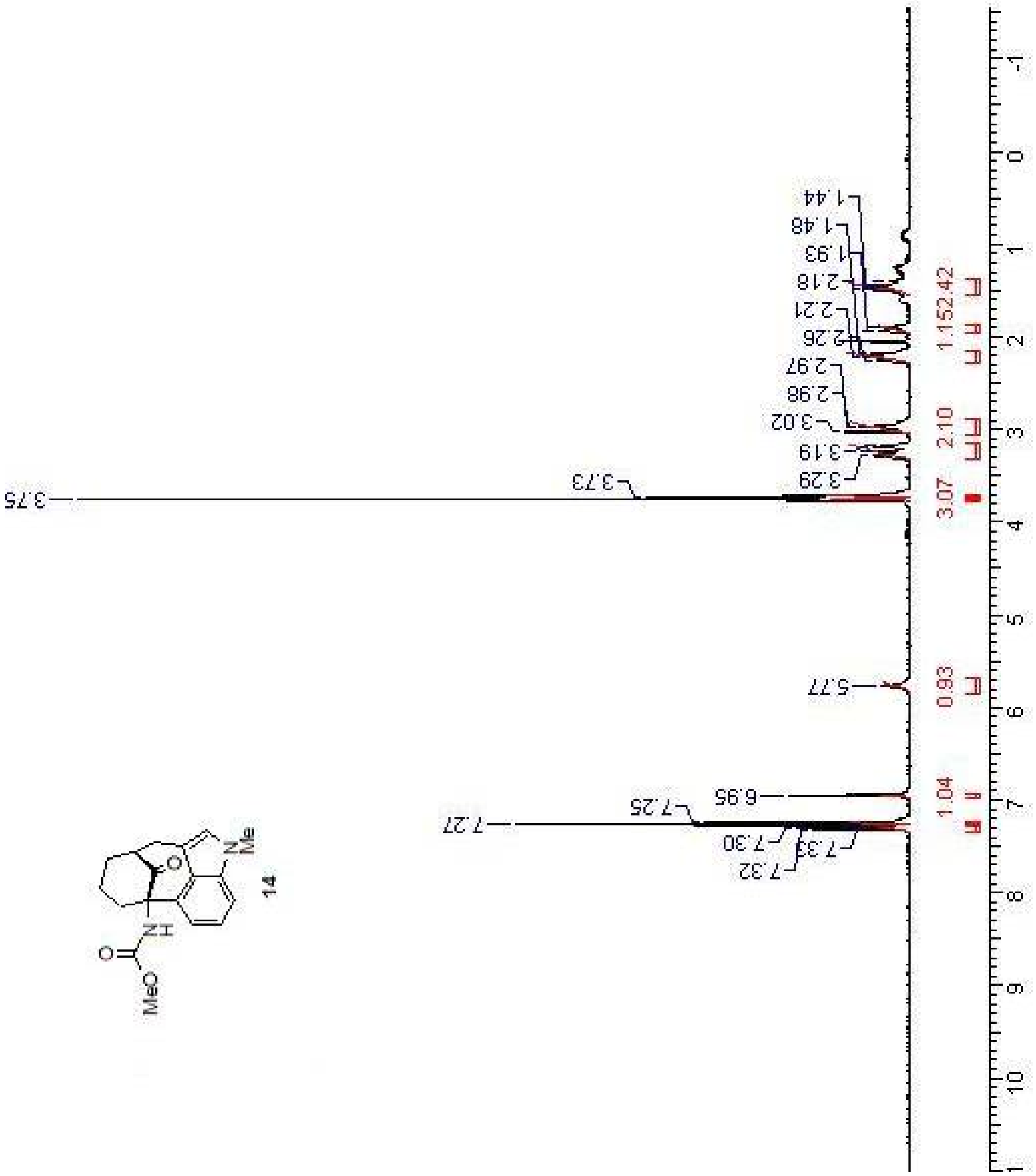

0.02
1.36
1.38
1.71
2.35
2.37
2.39
2.40
2.80
2.85
3.24
3.29
3.73
6.90
7.18
7.27
7.28
7.30
7.76
7.79
9.15
3.27
0.92
1.97
1.00
2.18
0.99
1.05
-2
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
TMS
O
N
Me
Se
12

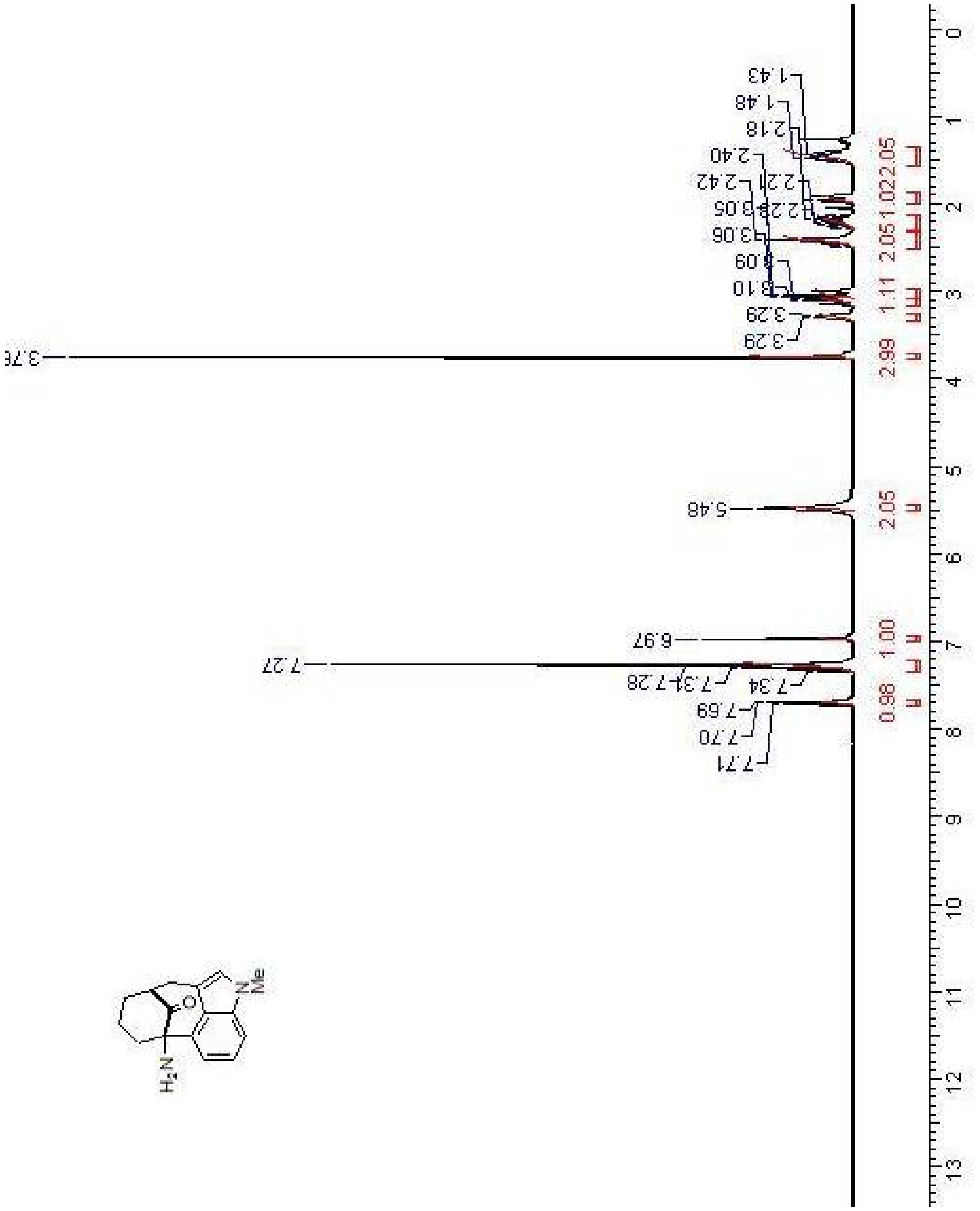

1.2620
1.2803
1.2884
1.4050
1.4101
1.4167
1.4226
1.9360
1.9411
2.1435
2.1927
2.1978
2.2198
2.2249
2.6349
2.6430
2.6620
2.6694
3.0097
3.0170
3.0412
3.0485
3.1446
3.1762
3.1945
3.2018
3.2099
3.7489
3.8472
6.7126
6.7192
6.7221
6.7295
6.9517
7.2143
7.2179
7.2245
1.19
1.13
0.97
1.13
1.14
1.07
3.20
1.03
0.99
2.00
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
MeO
O
O
N
Me

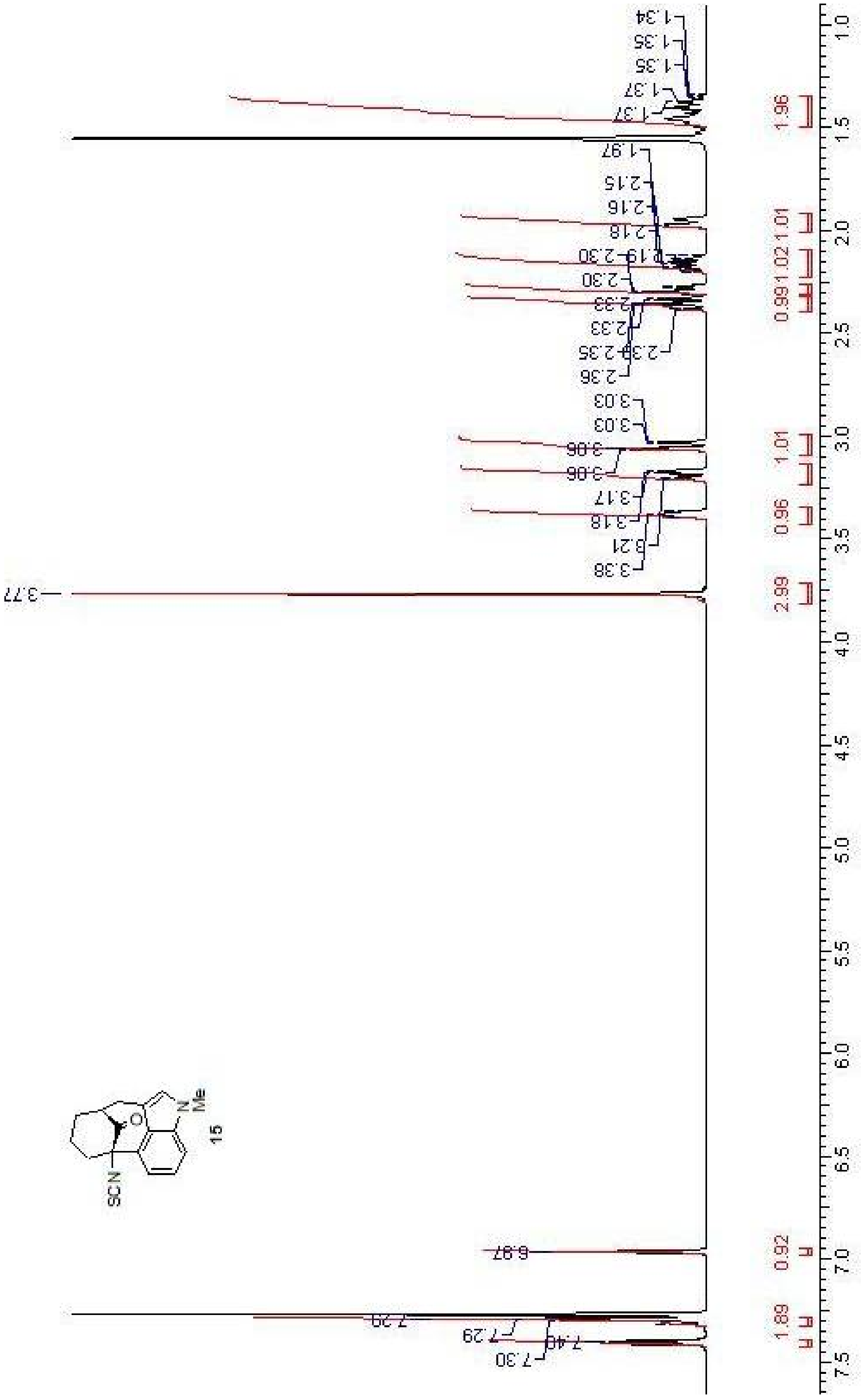

1.4271
1.4544
1.4638
1.4689
1.4912
1.5040
1.5211
1.9826
2.0108
2.1577
2.1706
2.1842
2.1979
2.4201
2.4278
2.4432
2.4509
3.0576
3.0636
3.0884
3.0944
3.2422
3.2533
3.2850
3.3115
3.7610
6.9752
7.2273
7.2110
7.2632
7.2700
7.2794
0.98
1.01
1.01
2.03
1.02
1.07
3.01
0.97
2.63
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
HOOC
O
N
Me

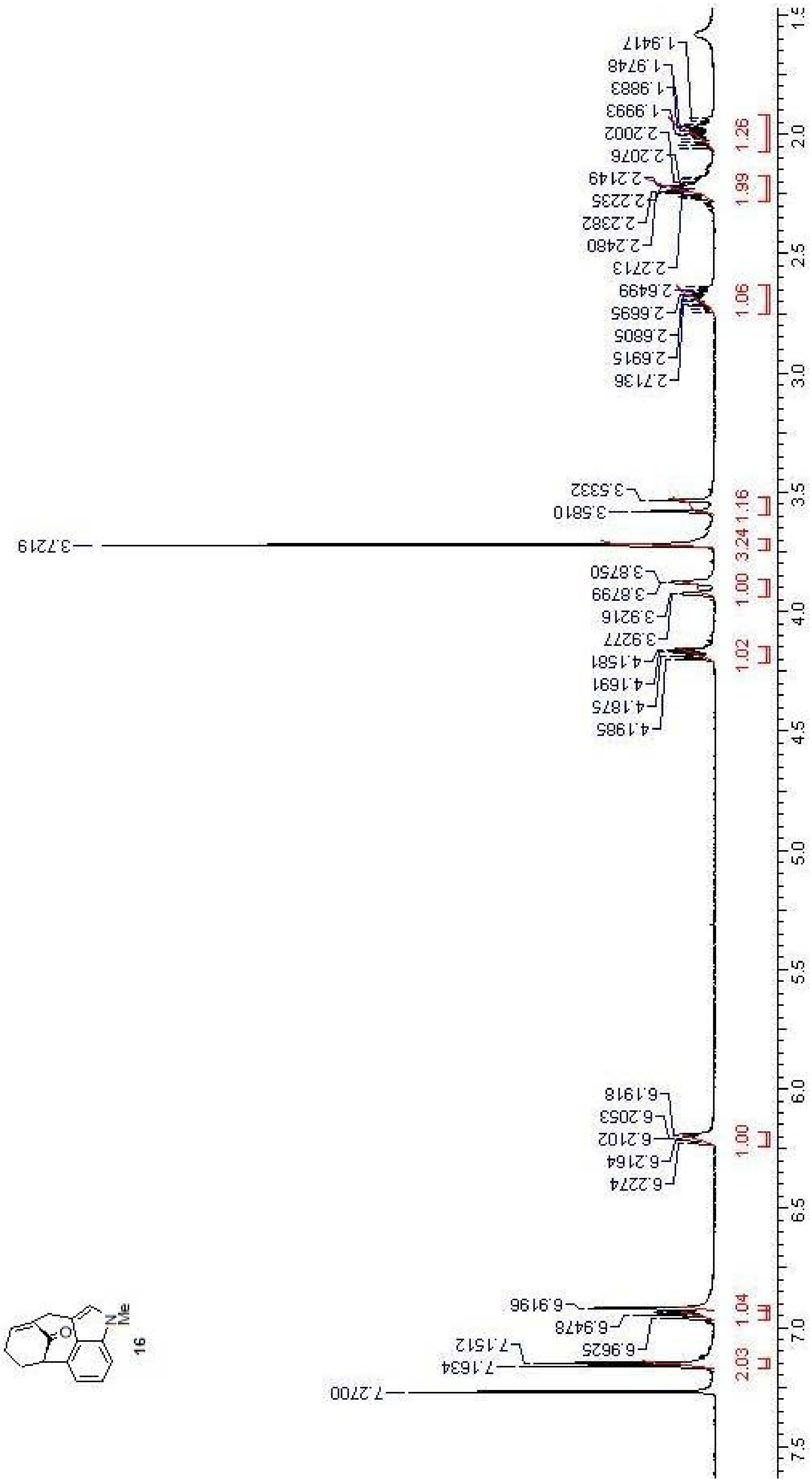

1.36
1.44
1.45
1.47
1.58
1.97
1.97
1.98
2.09
2.10
2.12
2.13
3.04
3.07
3.42
3.44
3.46
3.76
6.85
6.86
6.87
6.93
6.94
7.26
7.26
7.27
1.14
2.06
2.05
1.01
3.01
1.01
1.84
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
O
O
HN
N3
NMe

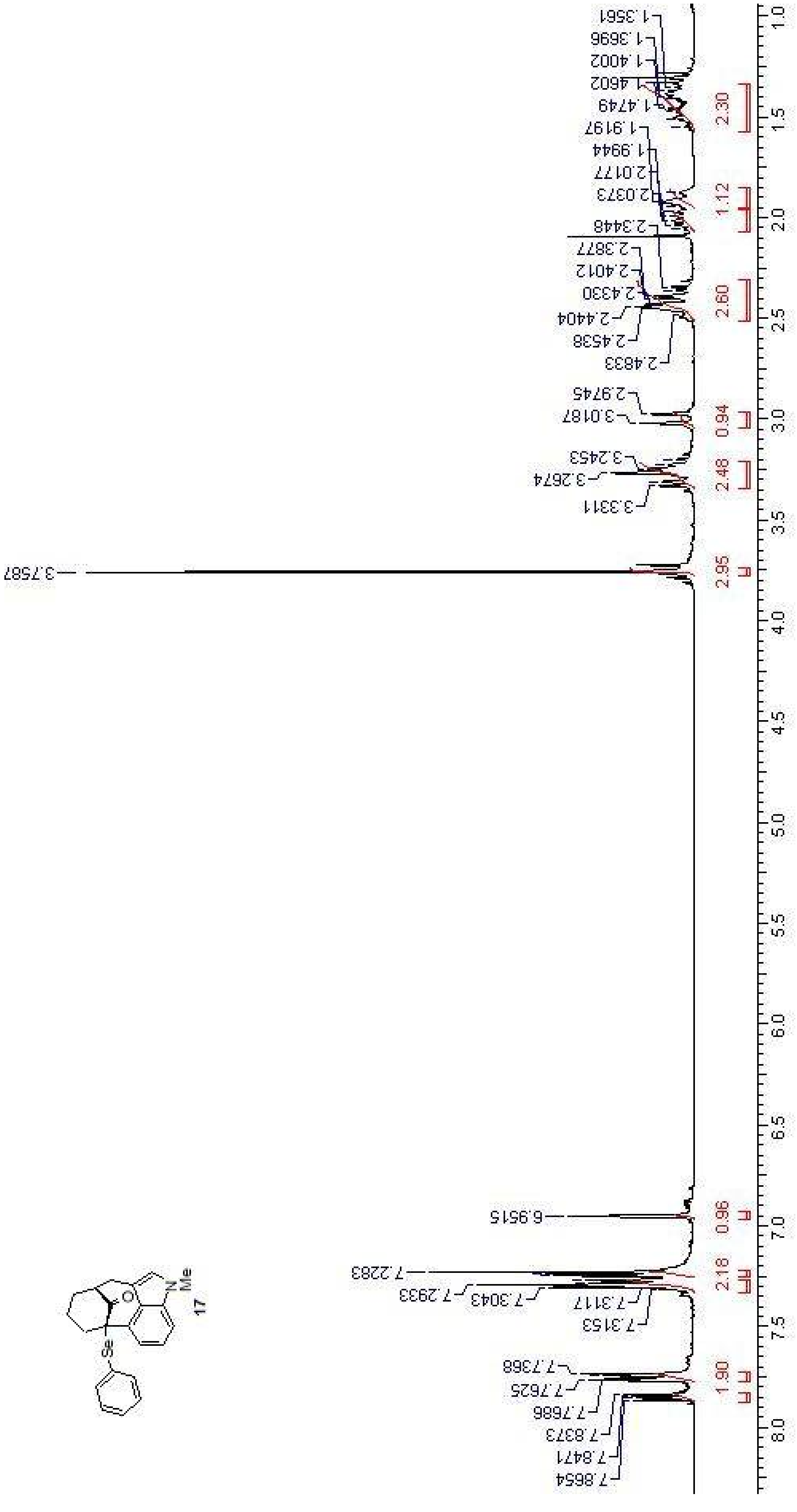
13

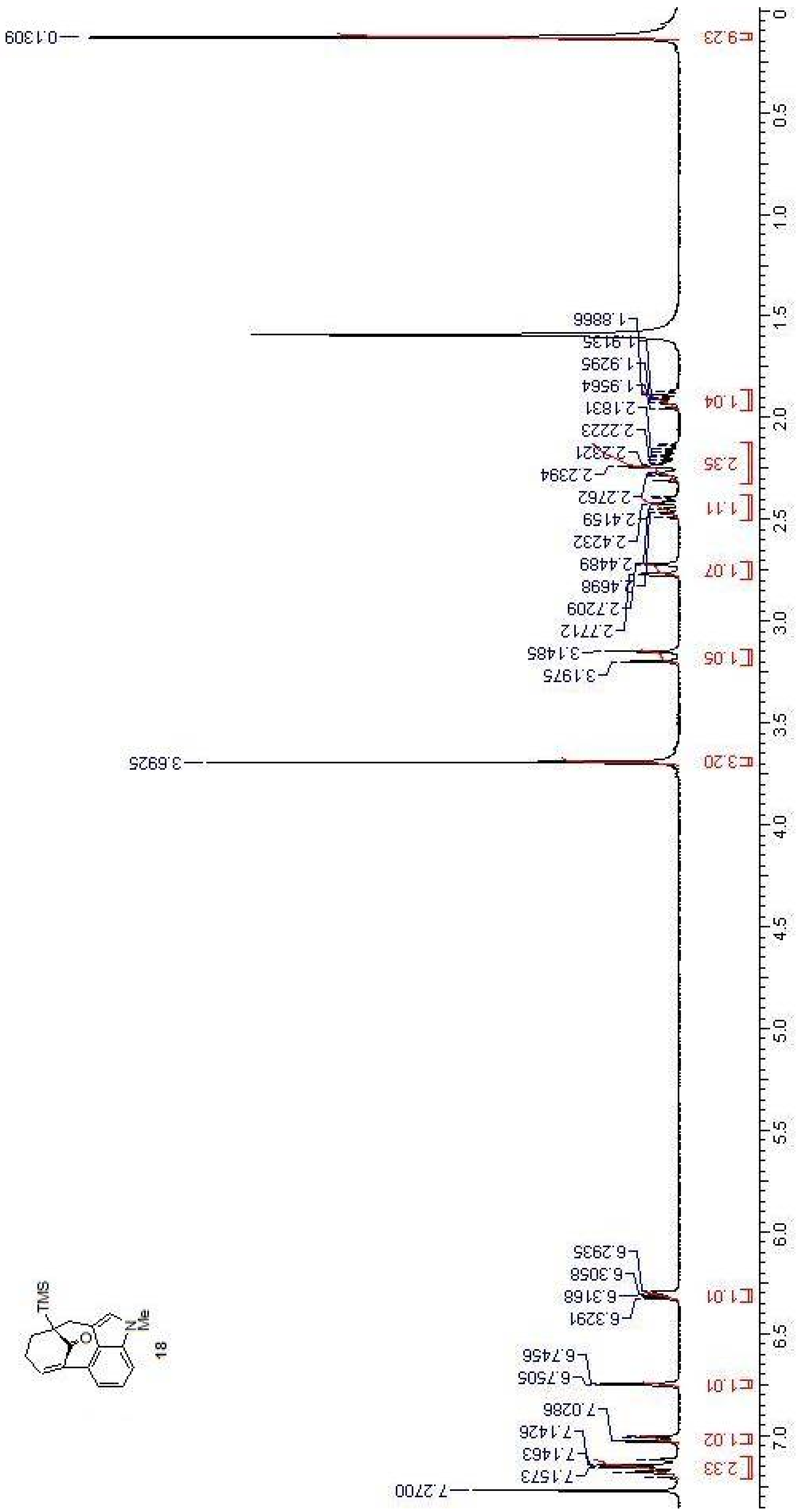

1.44
1.48
1.93
2.18
2.21
2.26
2.97
2.98
3.02
3.19
3.29
3.73
3.75
5.77
6.95
7.25
7.27
7.30
7.32
7.33
1.15
2.42
2.10
3.07
0.93
1.04
-1
0
1
2
3
4
5
6
7
8
9
10
MeO
O
N
H
O
N
Me
14

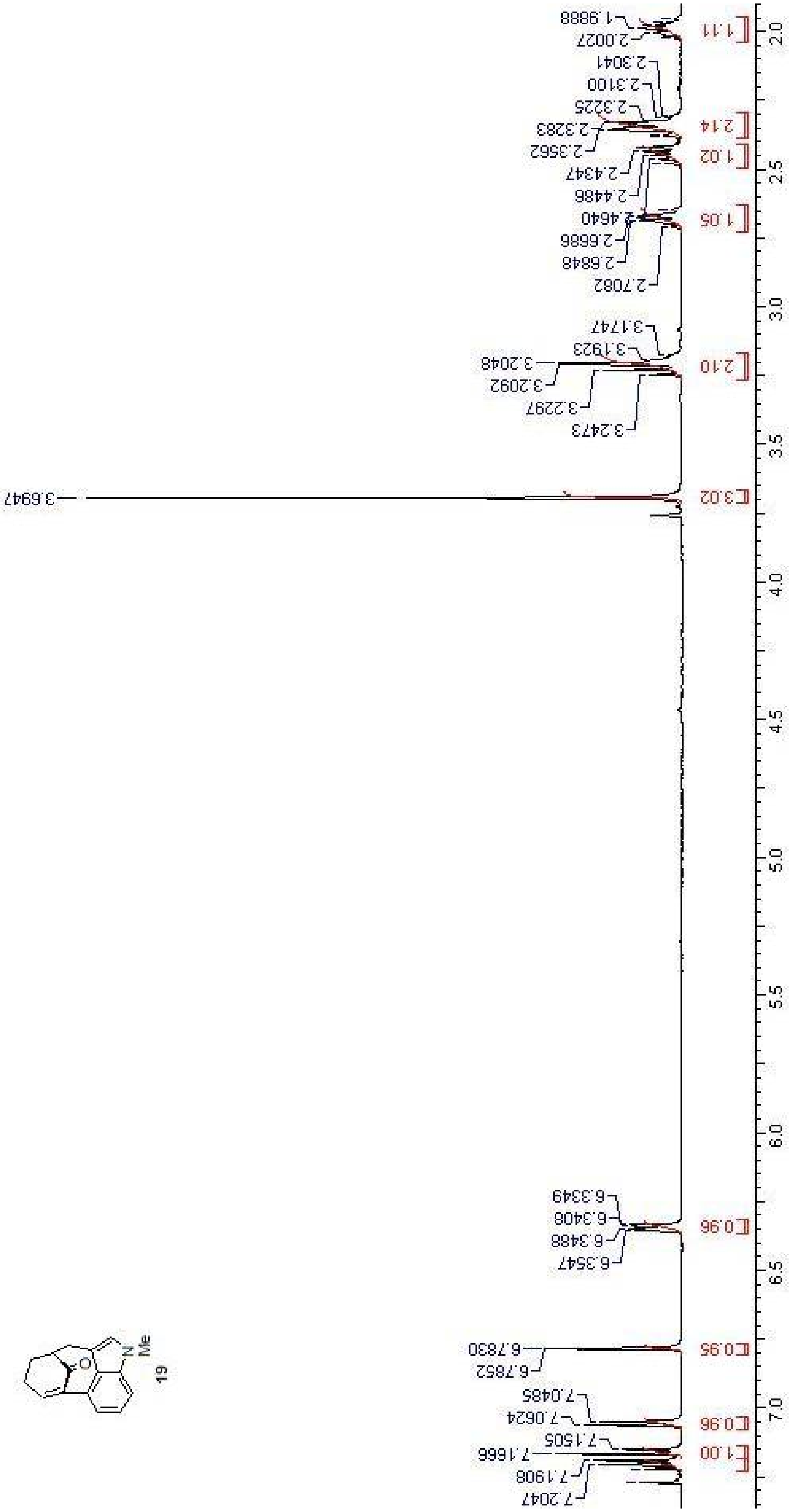

1.43
1.48
2.18
2.40
2.21
2.42
2.23
3.05
3.06
3.09
3.10
3.29
3.29
3.76
5.48
6.97
7.27
7.34
7.31
7.28
7.69
7.70
7.71
2.05
1.02
2.05
1.11
2.99
2.05
1.00
0.98
0
1
2
3
4
5
6
7
8
9
10
11
12
13
H₂N
O
N
Me


1.34
1.35
1.35
1.37
1.37
1.97
2.15
2.16
2.18
2.19
2.30
2.30
2.33
2.33
2.33
2.35
2.36
3.03
3.03
3.06
3.06
3.17
3.18
3.21
3.38
3.77
6.97
7.29
7.29
7.30
7.40
1.96
0.99
1.02
1.01
1.01
0.96
2.99
0.92
1.89
SCN
O
N
Me
15
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5

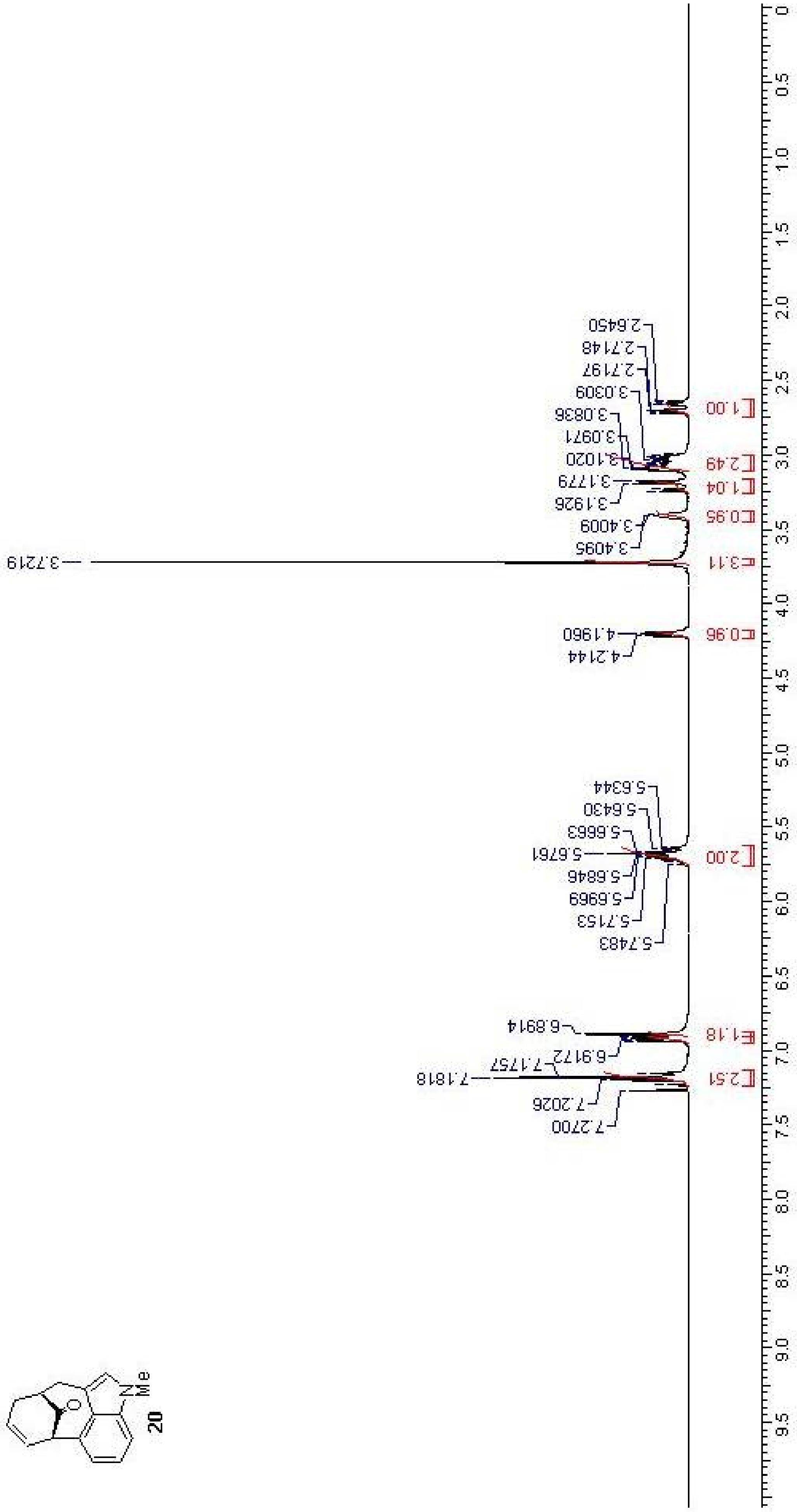

16
N
Me
O
7.2700
7.1634
7.1512
6.9625
6.9478
6.9196
6.2274
6.2164
6.2102
6.2053
6.1918
4.1985
4.1875
4.1691
4.1581
3.9277
3.9216
3.8799
3.8750
3.7219
3.5810
3.5332
2.7136
2.6915
2.6805
2.6695
2.6499
2.2713
2.2480
2.2382
2.2235
2.2149
2.2076
2.2002
1.9993
1.9883
1.9748
1.9417
2.03
1.04
1.00
1.02
1.00
3.24
1.16
1.06
1.99
1.26
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5


1.3561
1.3696
1.4002
1.4602
1.4749
1.9197
1.9944
2.0177
2.0373
2.3448
2.3877
2.4012
2.4330
2.4404
2.4538
2.4833
2.9745
3.0187
3.2453
3.2674
3.3311
3.7587
6.9515
7.2283
7.2933
7.3043
7.3117
7.3153
7.7368
7.7625
7.7686
7.8373
7.8471
7.8654
2.30
1.12
2.60
0.94
2.48
2.95
0.96
2.18
1.90
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
Se
O
N
Me
17

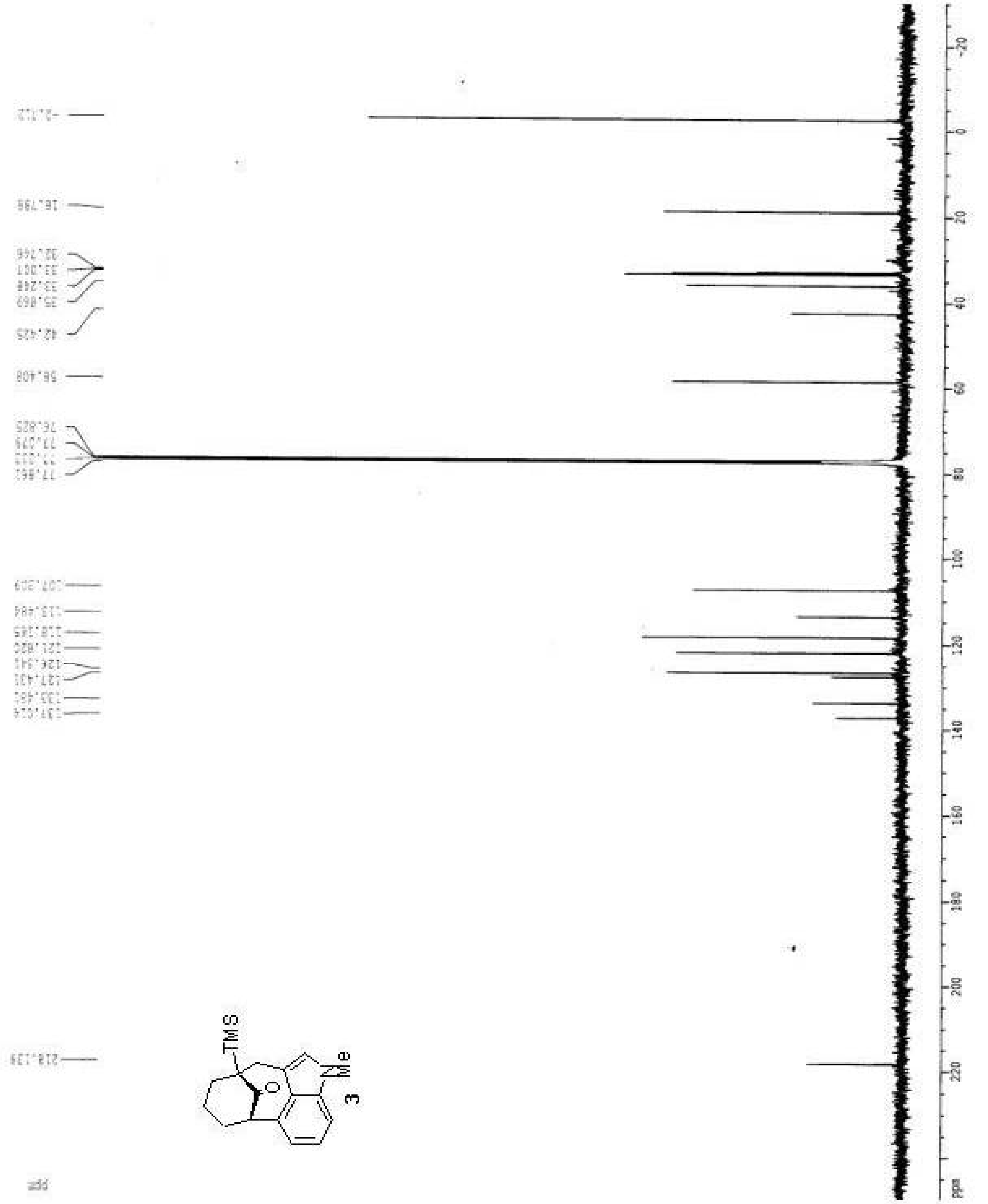

0.1309
1.8866
1.9135
1.9295
1.9564
2.1831
2.2223
2.2321
2.2394
2.2762
2.4159
2.4232
2.4489
2.4698
2.7209
2.7712
3.1485
3.1975
3.6925
6.2935
6.3058
6.3168
6.3291
6.7456
6.7505
7.0286
7.1426
7.1463
7.1573
7.2700
9.23
1.04
2.35
1.11
1.07
1.05
3.20
1.01
1.01
1.02
2.33
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
TMS
O
N
Me
18


1.9888
2.0027
2.3041
2.3100
2.3225
2.3283
2.3562
2.4347
2.4486
2.4640
2.6686
2.6848
2.7082
3.1747
3.1923
3.2048
3.2092
3.2297
3.2473
3.6947
6.3349
6.3408
6.3488
6.3547
6.7830
6.7852
7.0485
7.0624
7.1505
7.1666
7.1908
7.2047
1.11
2.14
1.02
1.05
2.10
3.02
0.96
0.95
0.96
1.00
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
O
N
Me

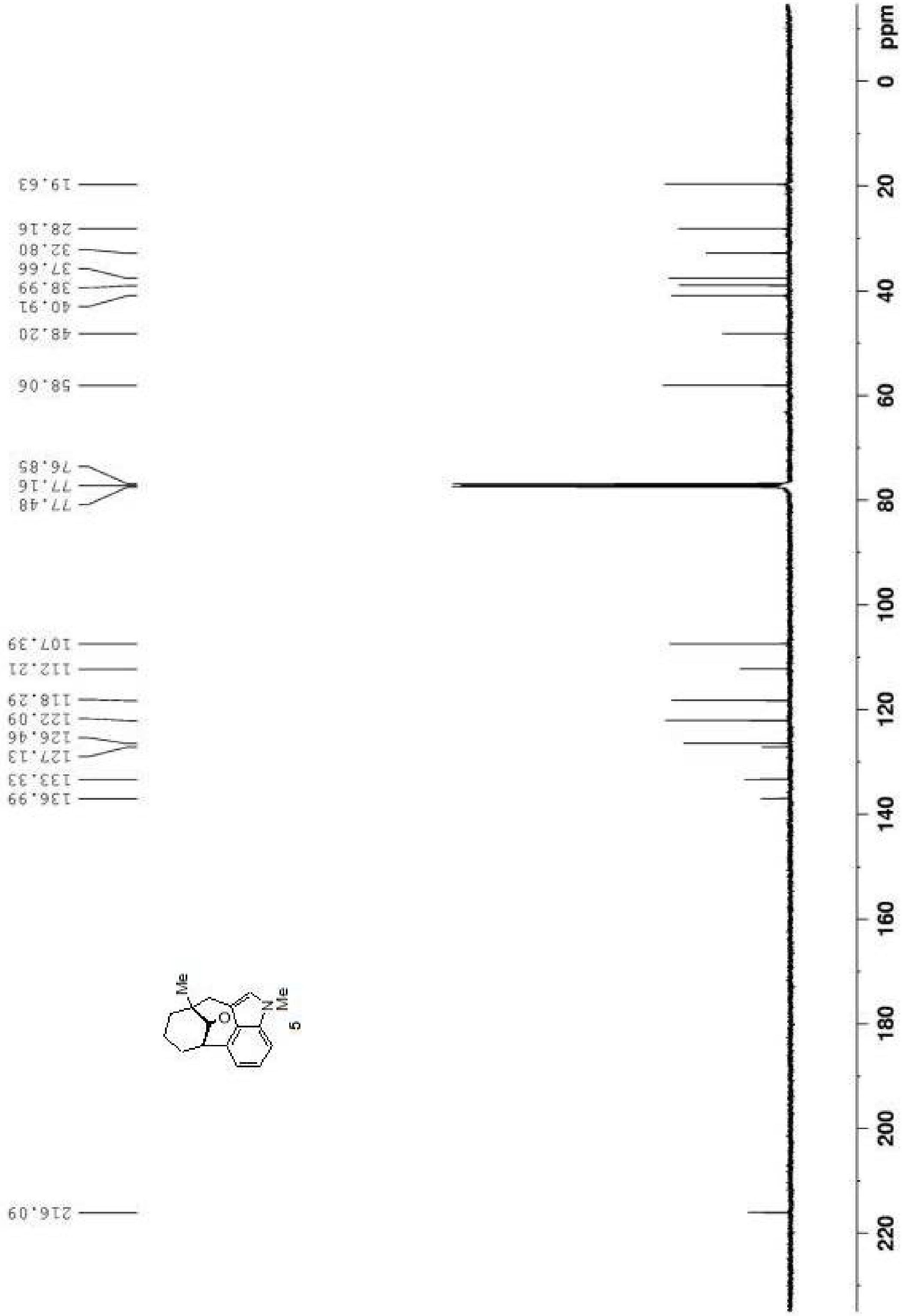
19


2.6450
2.7148
2.7197
3.0309
3.0836
3.0971
3.1020
3.1779
3.1926
3.4009
3.4095
3.7219
4.1960
4.2144
5.6344
5.6430
5.6663
5.6761
5.6846
5.6969
5.7153
5.7483
6.8914
6.9172
7.1757
7.1818
7.2026
7.2700
1.00
2.49
1.04
0.95
3.11
0.96
2.00
1.18
2.51
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
O
N
Me

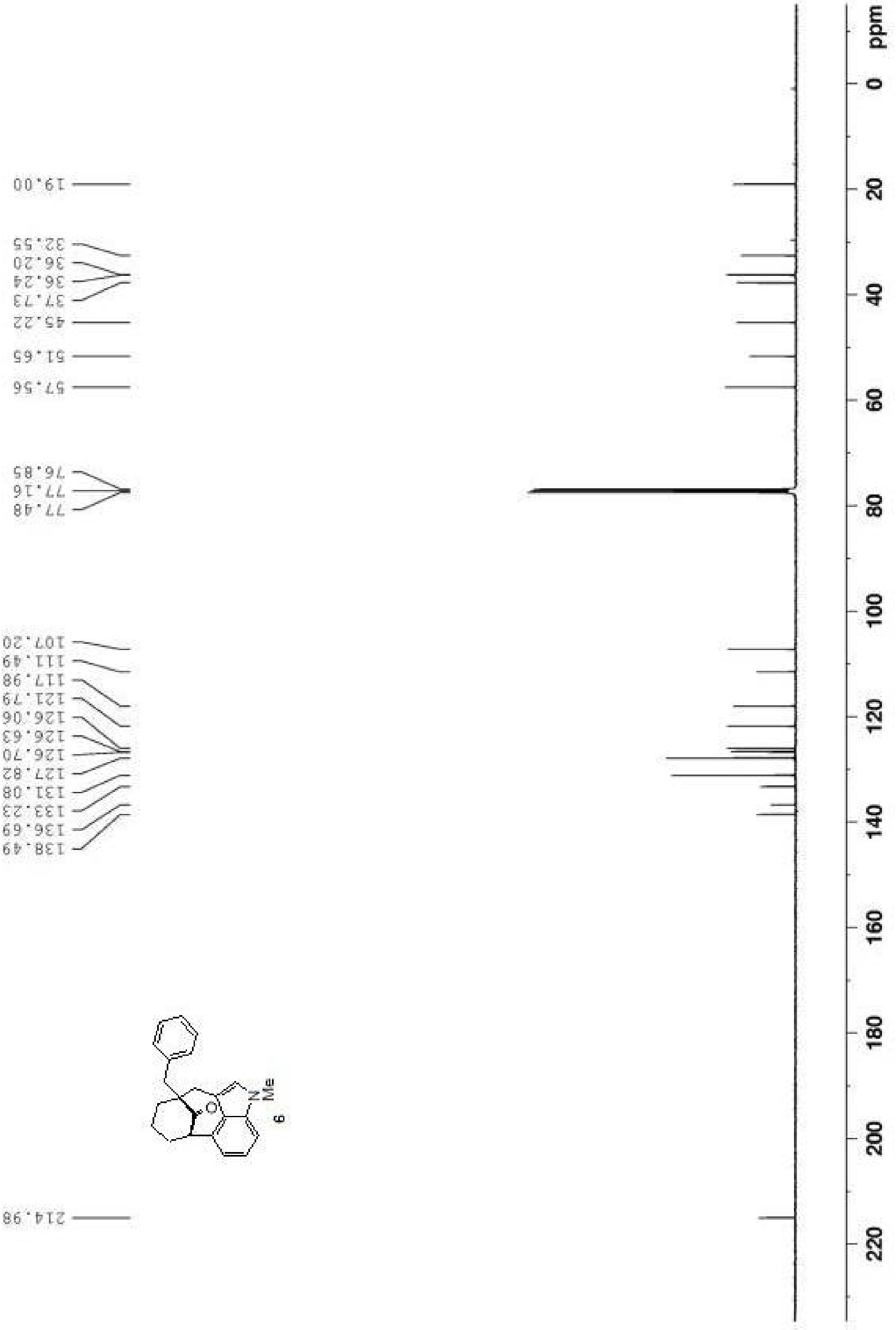
20

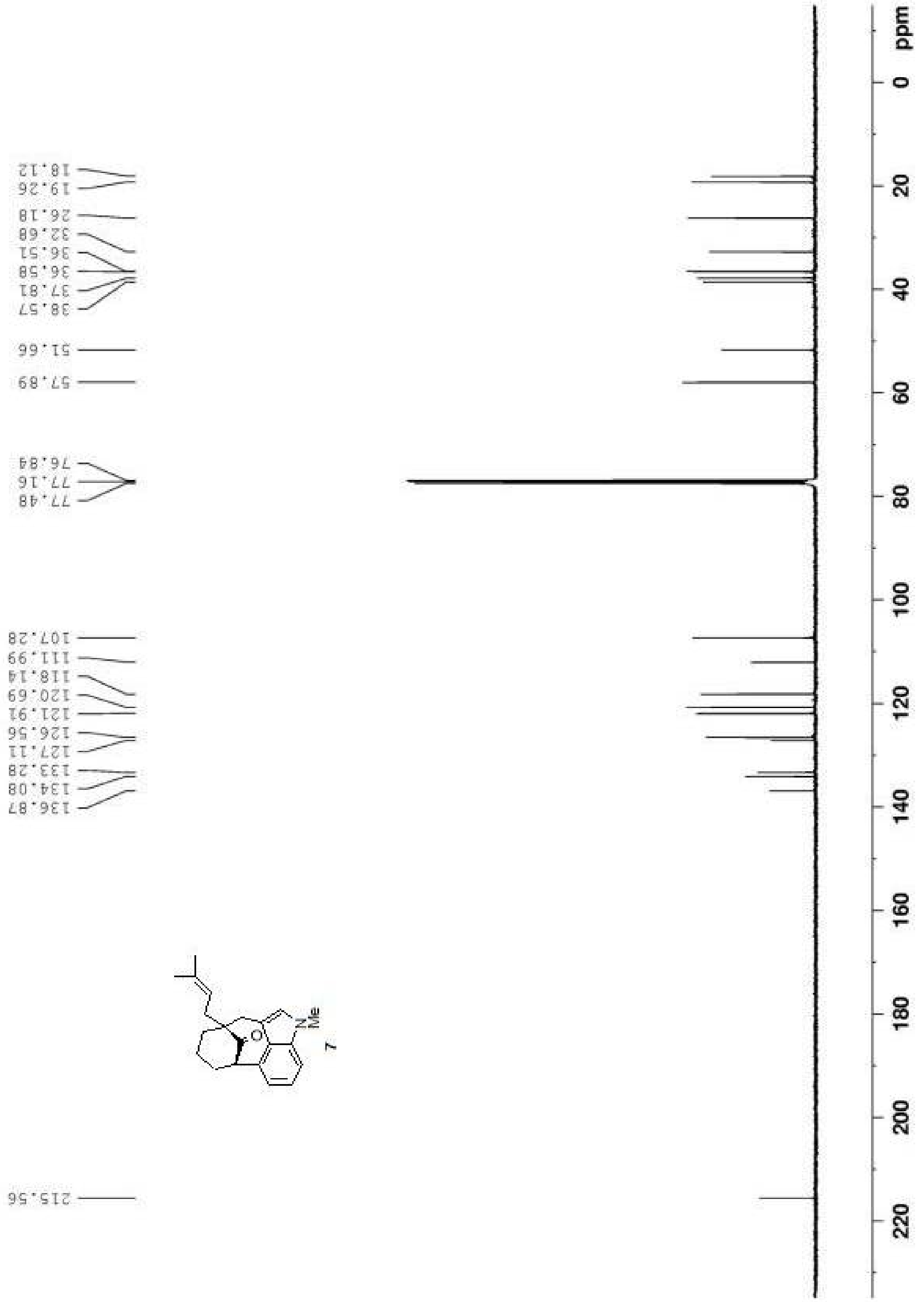

-2.712
16.796
32.746
33.001
33.248
35.869
42.425
56.408
76.825
77.079
77.333
77.861
107.309
113.486
118.185
121.880
126.541
127.431
135.481
137.014
218.139
ppm
TMS
O
N
Me
3
-20
0
20
40
60
80
100
120
140
160
180
200
220
ppm


-2.22
-2.15
0.59
18.96
32.70
33.08
34.93
37.47
43.30
54.06
76.84
77.16
77.48
106.97
114.05
117.87
121.38
126.34
128.81
137.38
137.75
221.75
TMS
TMS
O
Me
4
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230

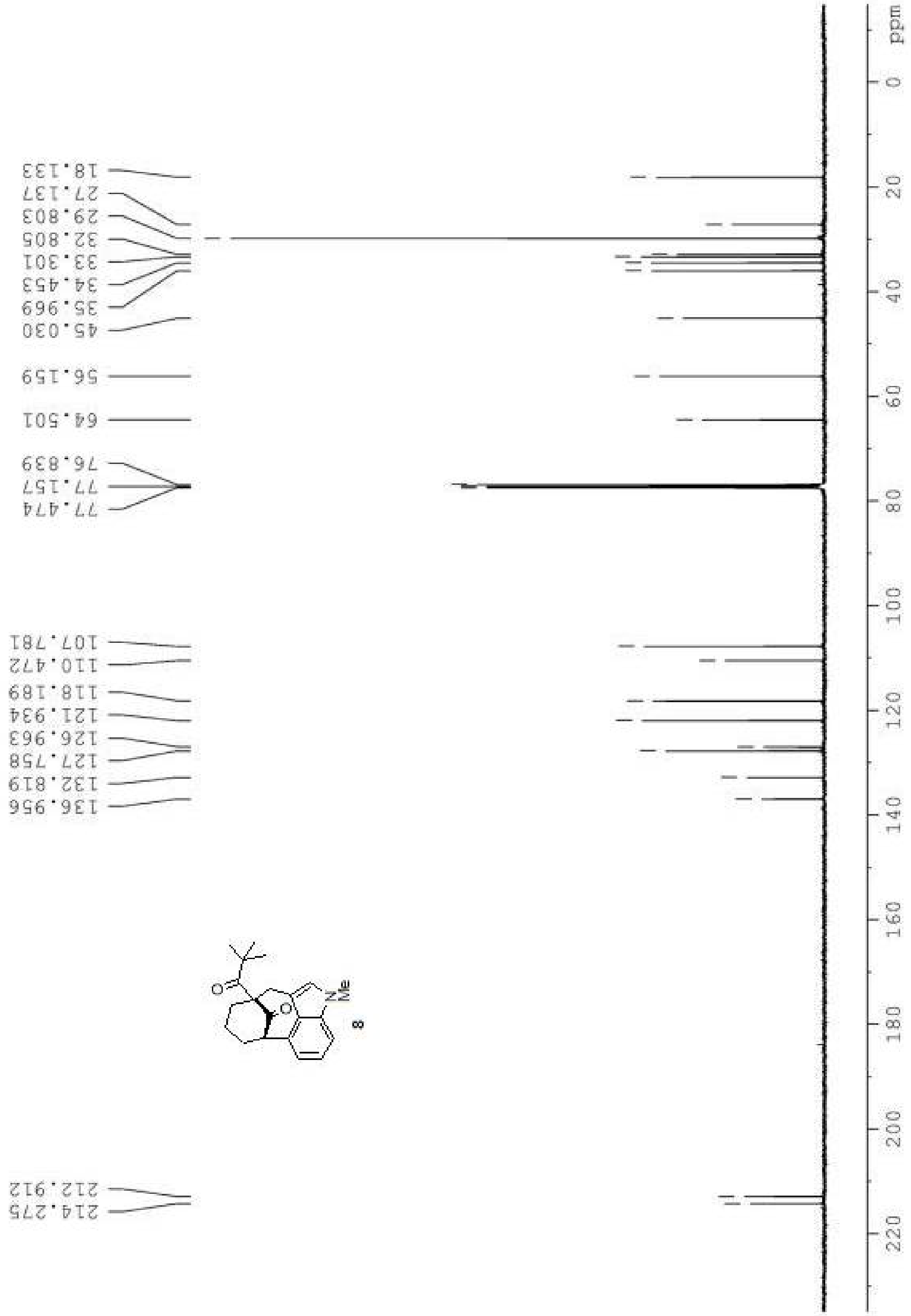

19.63
28.16
32.80
37.66
38.99
40.91
48.20
58.06
76.85
77.16
77.48
107.39
112.21
118.29
122.09
126.46
127.13
133.33
136.99
216.09
Me
O
N
Me
ppm
0
20
40
60
80
100
120
140
160
180
200
220

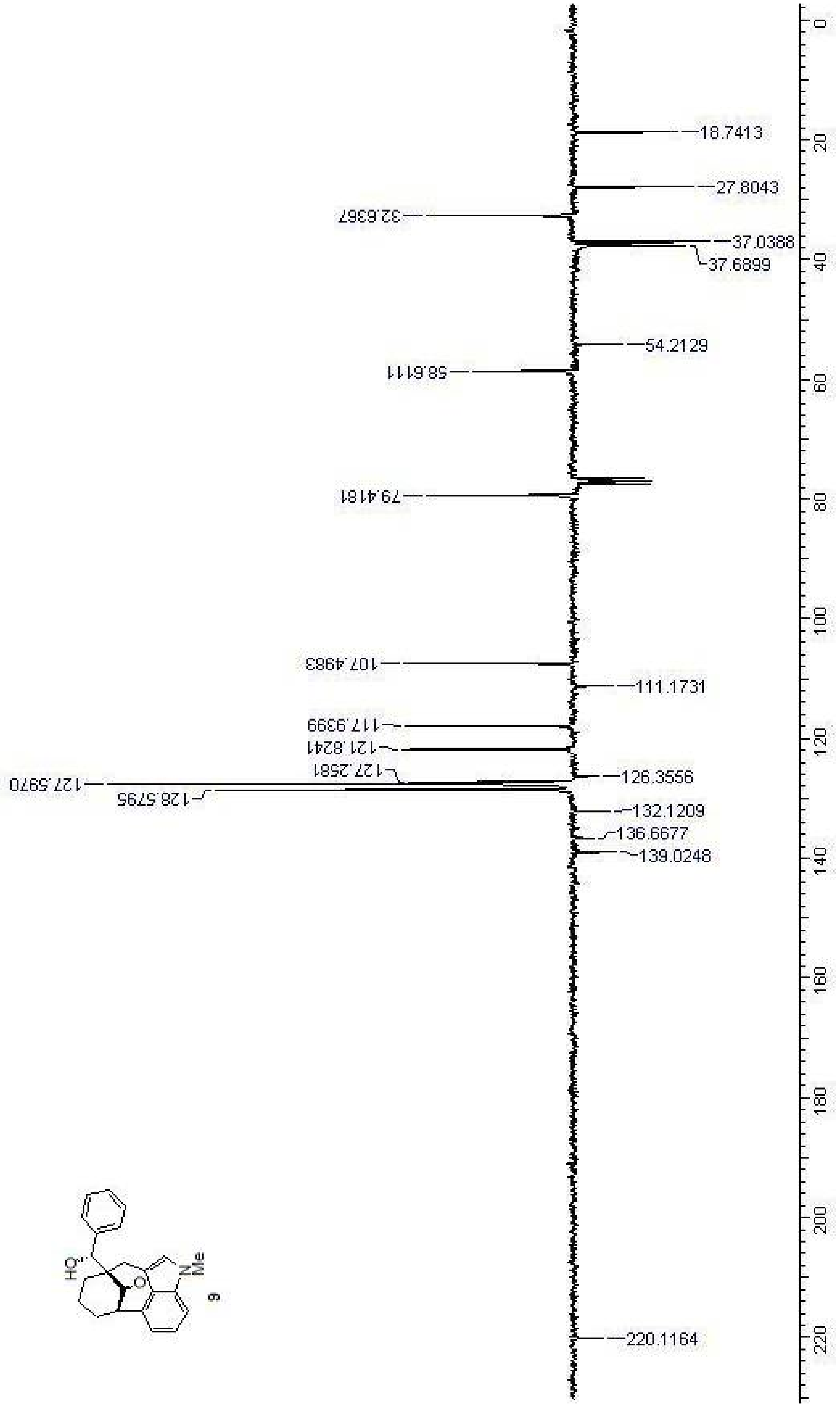
5

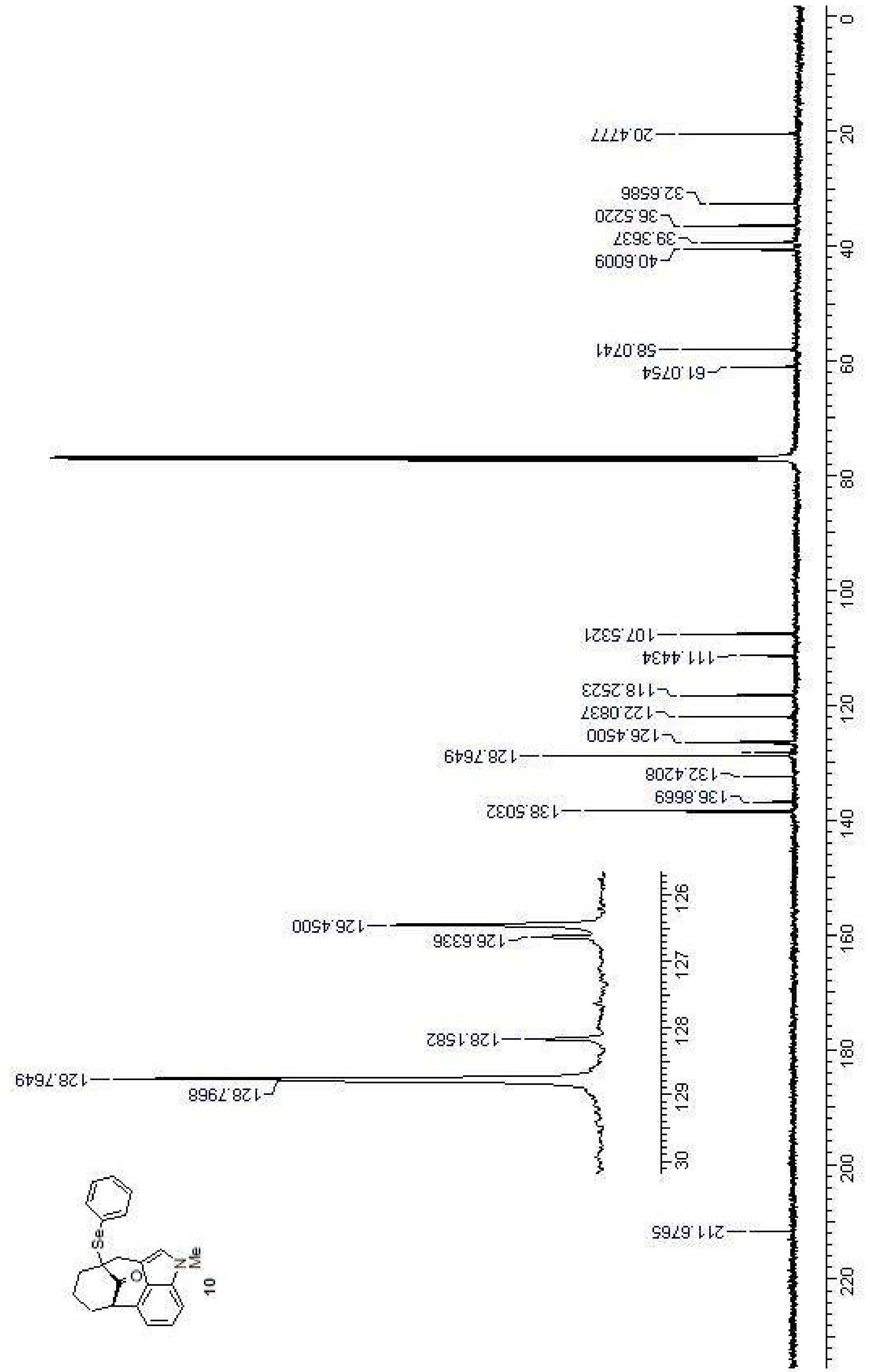

19.00
32.55
36.20
36.24
37.73
45.22
51.65
57.56
76.85
77.16
77.48
107.20
111.49
117.98
121.79
126.06
126.63
126.70
127.82
131.08
133.23
136.69
138.49
214.98
O
N
Me
6
ppm
0
20
40
60
80
100
120
140
160
180
200
220

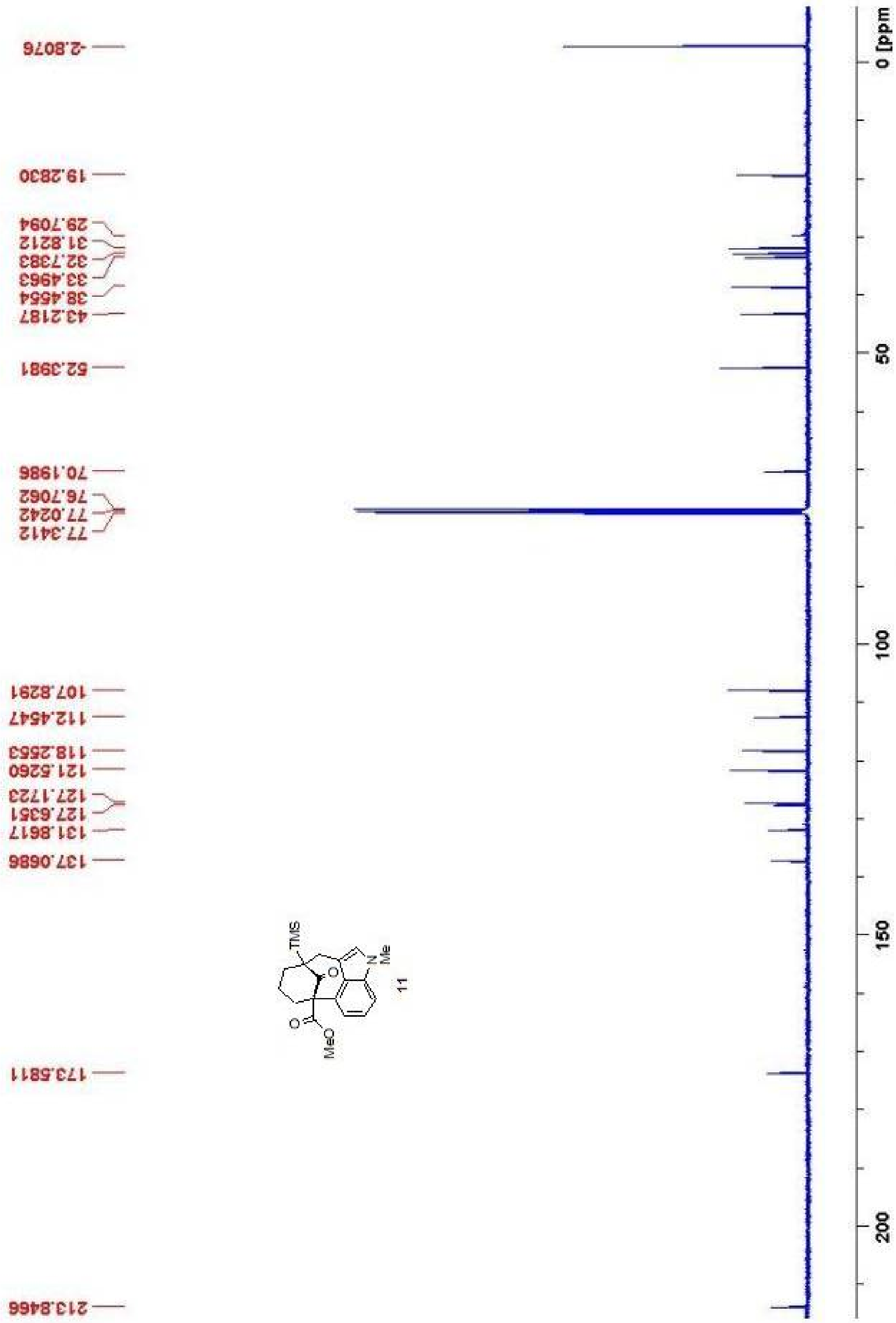

18.12
19.26
26.18
32.68
36.51
36.58
37.81
38.57
51.66
57.89
76.84
77.16
77.48
107.28
111.99
118.14
120.69
121.91
126.56
127.11
133.28
134.08
136.87
215.56
O
N
Me
ppm
0
20
40
60
80
100
120
140
160
180
200
220

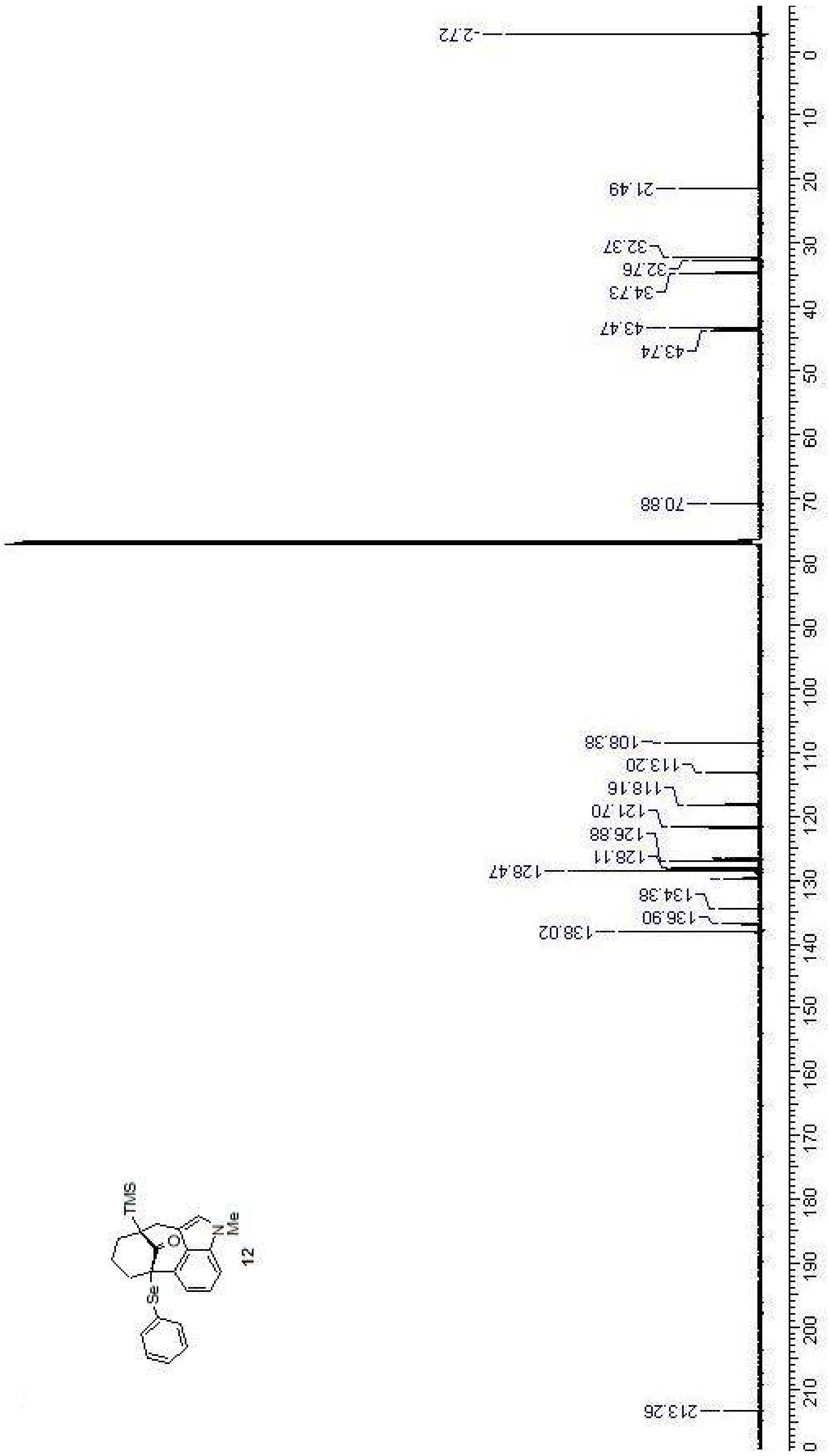
7

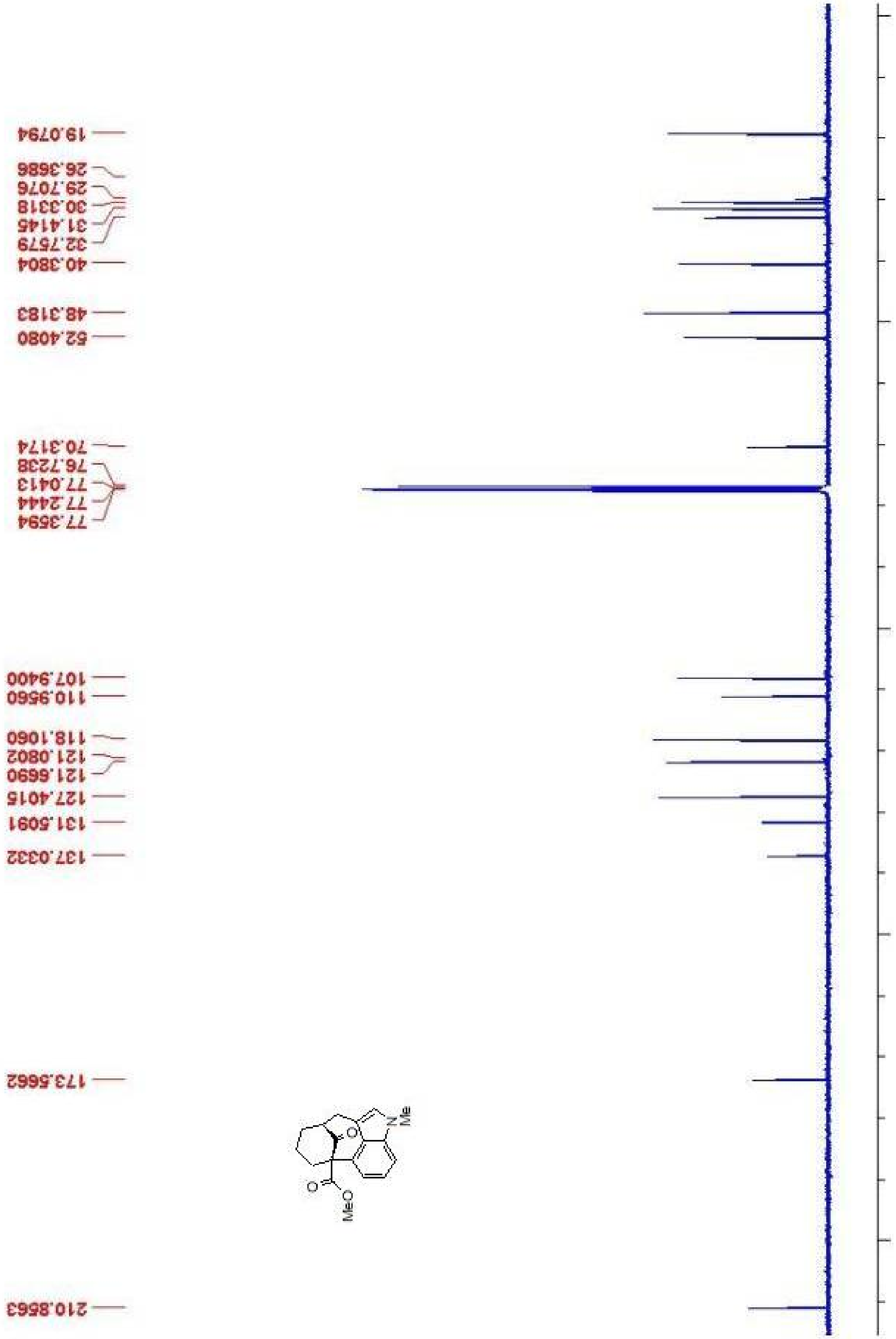

18.133
27.137
29.803
32.805
33.301
34.453
35.969
45.030
56.159
64.501
76.839
77.157
77.474
107.781
110.472
118.189
121.934
126.963
127.758
132.819
136.956
212.912
214.275
O
O
N
Me
8
ppm
0
20
40
60
80
100
120
140
160
180
200
220

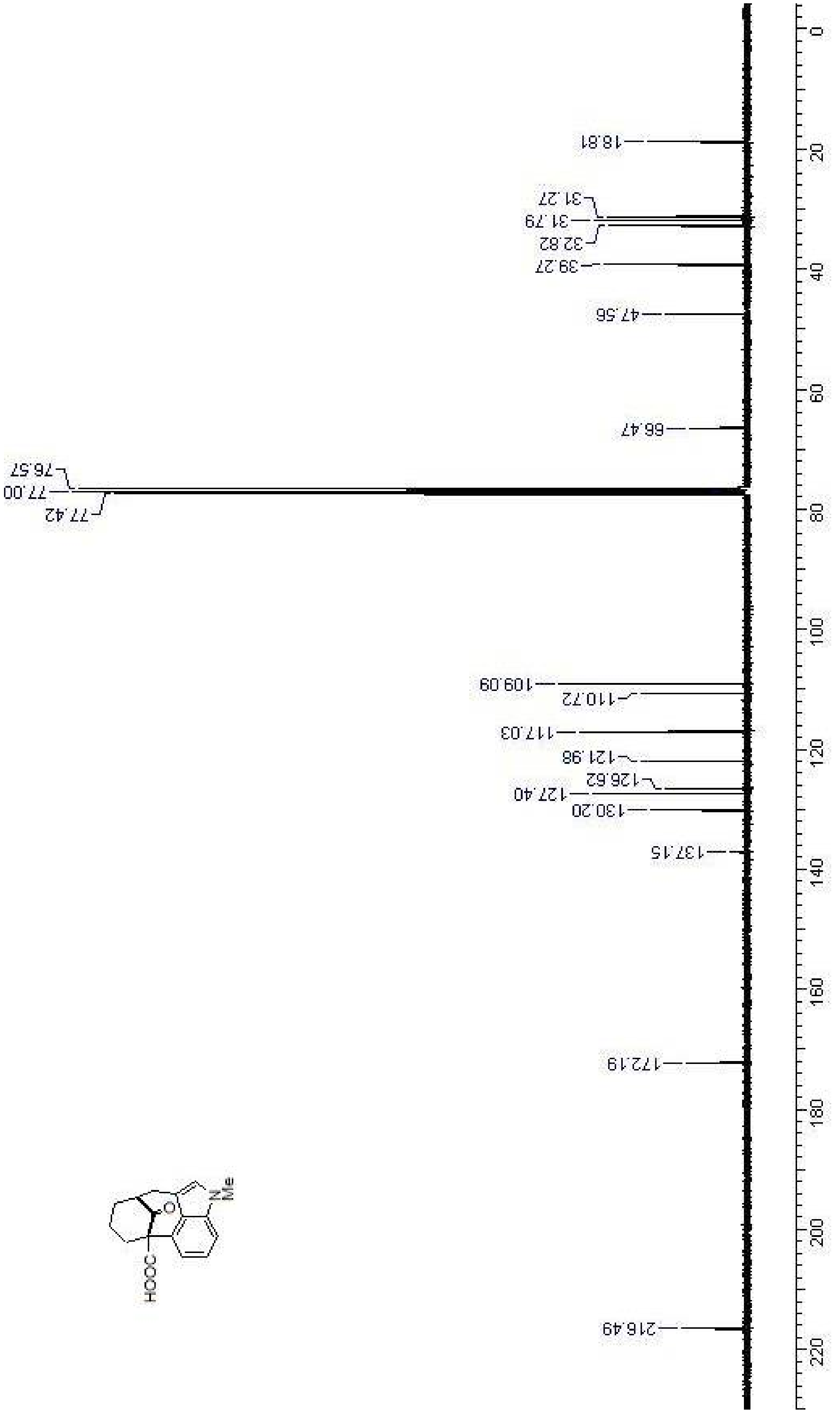

18.7413
27.8043
32.6367
37.0388
37.6899
54.2129
58.6111
79.4181
107.4983
111.1731
117.9399
121.8241
127.2581
126.3556
127.5970
128.5795
132.1209
136.6677
139.0248
220.1164
0
20
40
60
80
100
120
140
160
180
200
220
HO
O
N
Me
9

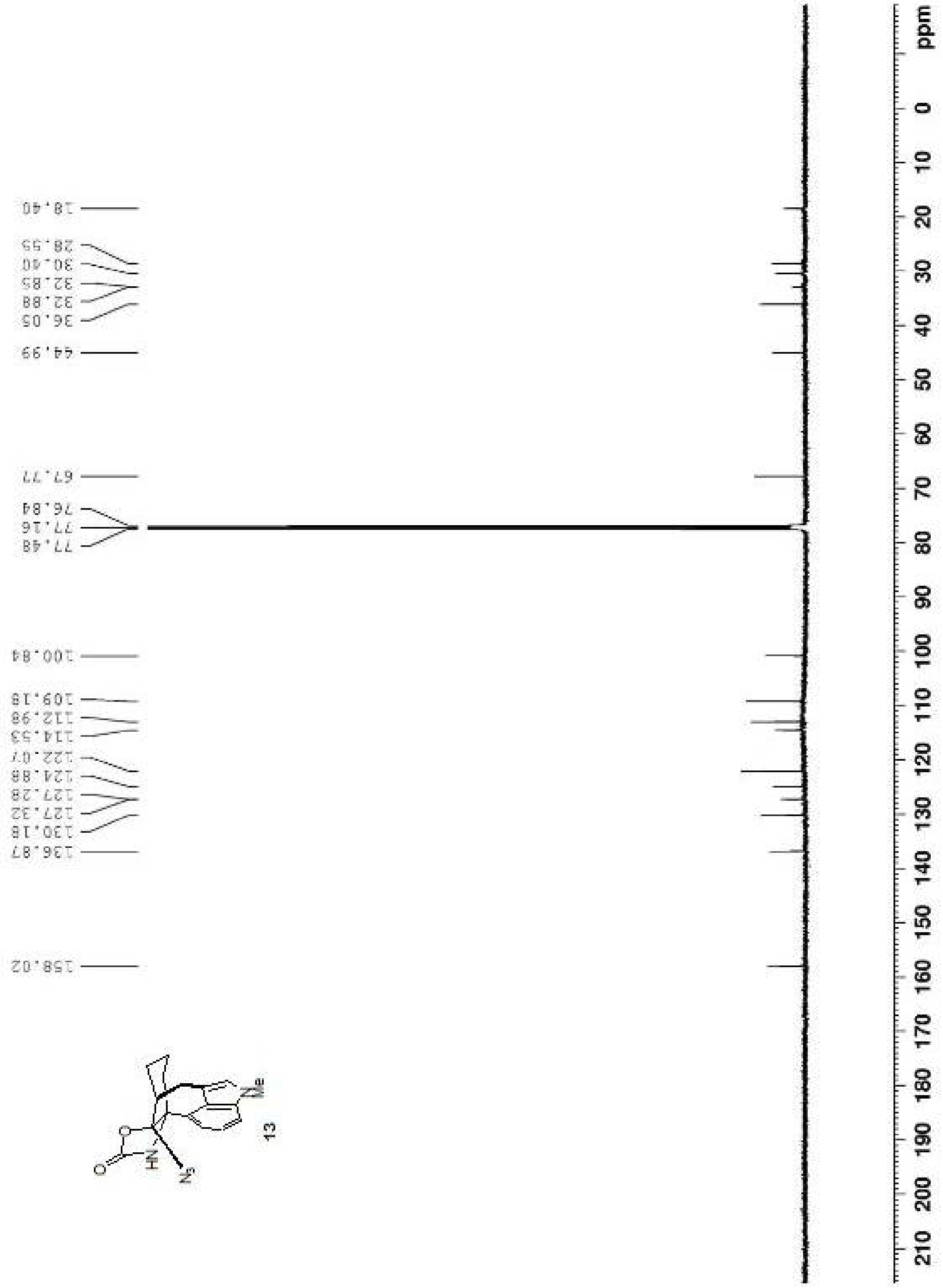

20.4777
32.6586
36.5220
39.3637
40.6009
58.0741
61.0754
107.5321
111.4434
118.2523
122.0837
126.4500
128.7649
132.4208
136.8669
138.5032
211.6765
126.4500
126.6336
128.1582
128.7649
128.7968
126
127
128
129
30
0
20
40
60
80
100
120
140
160
180
200
220
Se
O
N
Me
10


-2.8076
19.2830
29.7094
31.8212
32.7383
33.4963
38.4554
43.2187
52.3981
70.1986
76.7062
77.0242
77.3412
107.8291
112.4547
118.2553
121.5260
127.1723
127.6351
131.8617
137.0686
173.5811
213.8466
TMS
O
N
Me
MeO
O
11
0
50
100
150
200
[ppm]

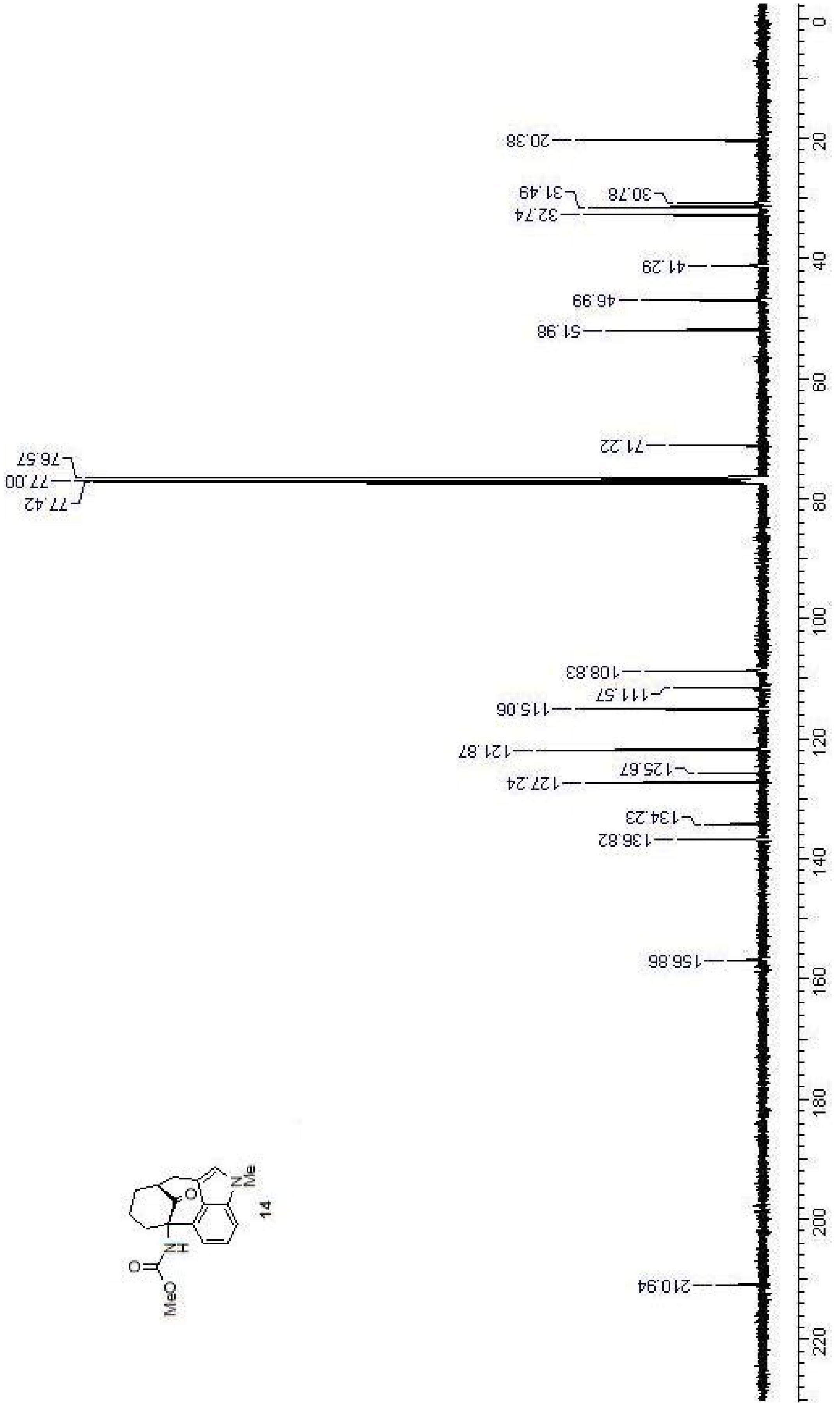

-2.72
21.49
32.37
32.76
34.73
43.47
43.74
70.88
108.38
113.20
118.16
121.70
126.88
128.11
128.47
134.38
136.90
138.02
213.26
TMS
O
N
Me
Se
12
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


19.0794
26.3686
29.7076
30.3318
31.4145
32.7579
40.3804
48.3183
52.4080
70.3174
76.7238
77.0413
77.2444
77.3594
107.9400
110.9560
118.1060
121.0802
121.6690
127.4015
131.5091
137.0332
173.5662
210.8563
MeO
O
O
N
Me

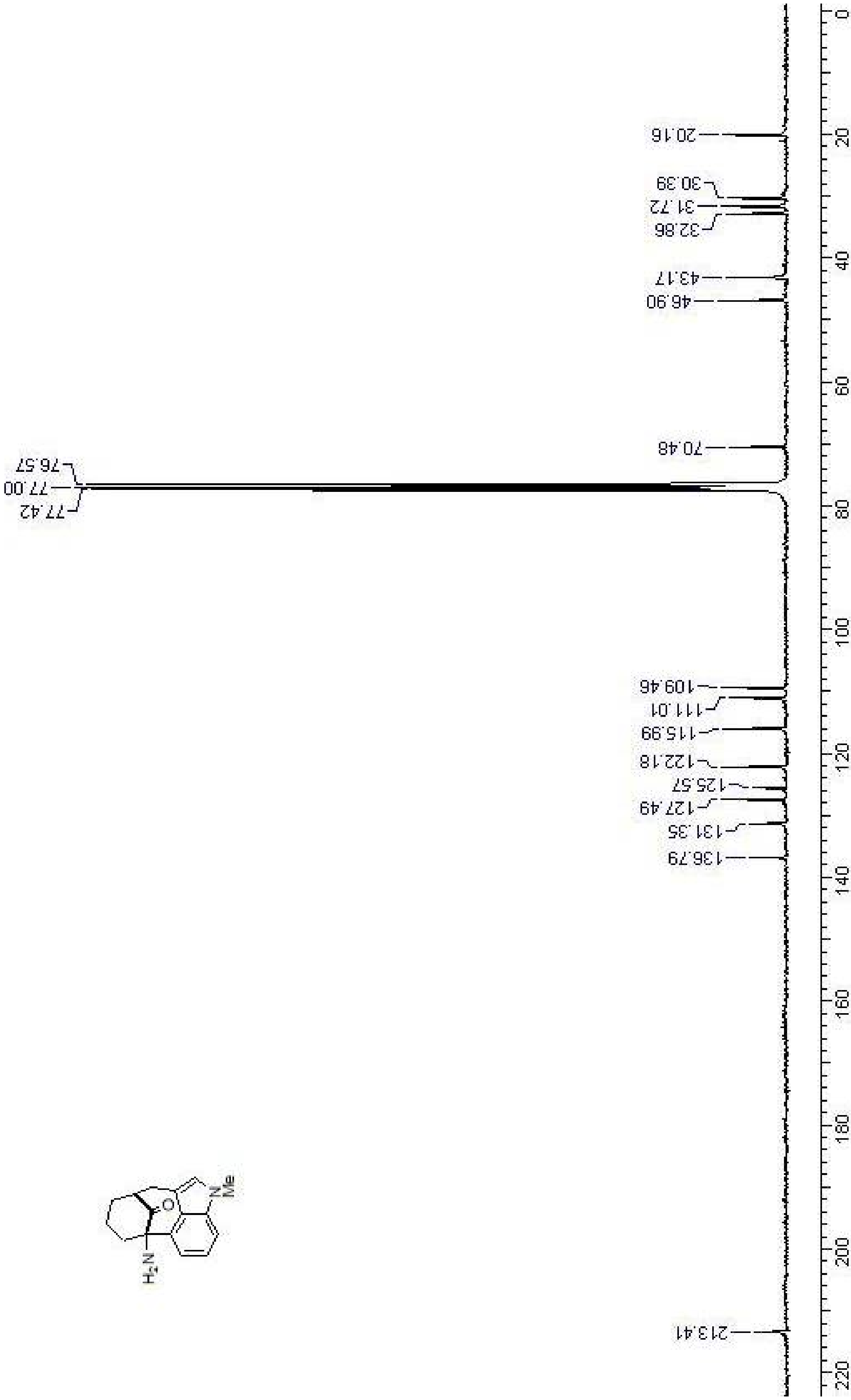

18.81
31.27
31.79
32.82
39.27
47.56
66.47
76.57
77.00
77.42
109.09
110.72
117.03
121.98
126.62
127.40
130.20
137.15
172.19
216.49
HOOC
O
N
Me
0
20
40
60
80
100
120
140
160
180
200
220

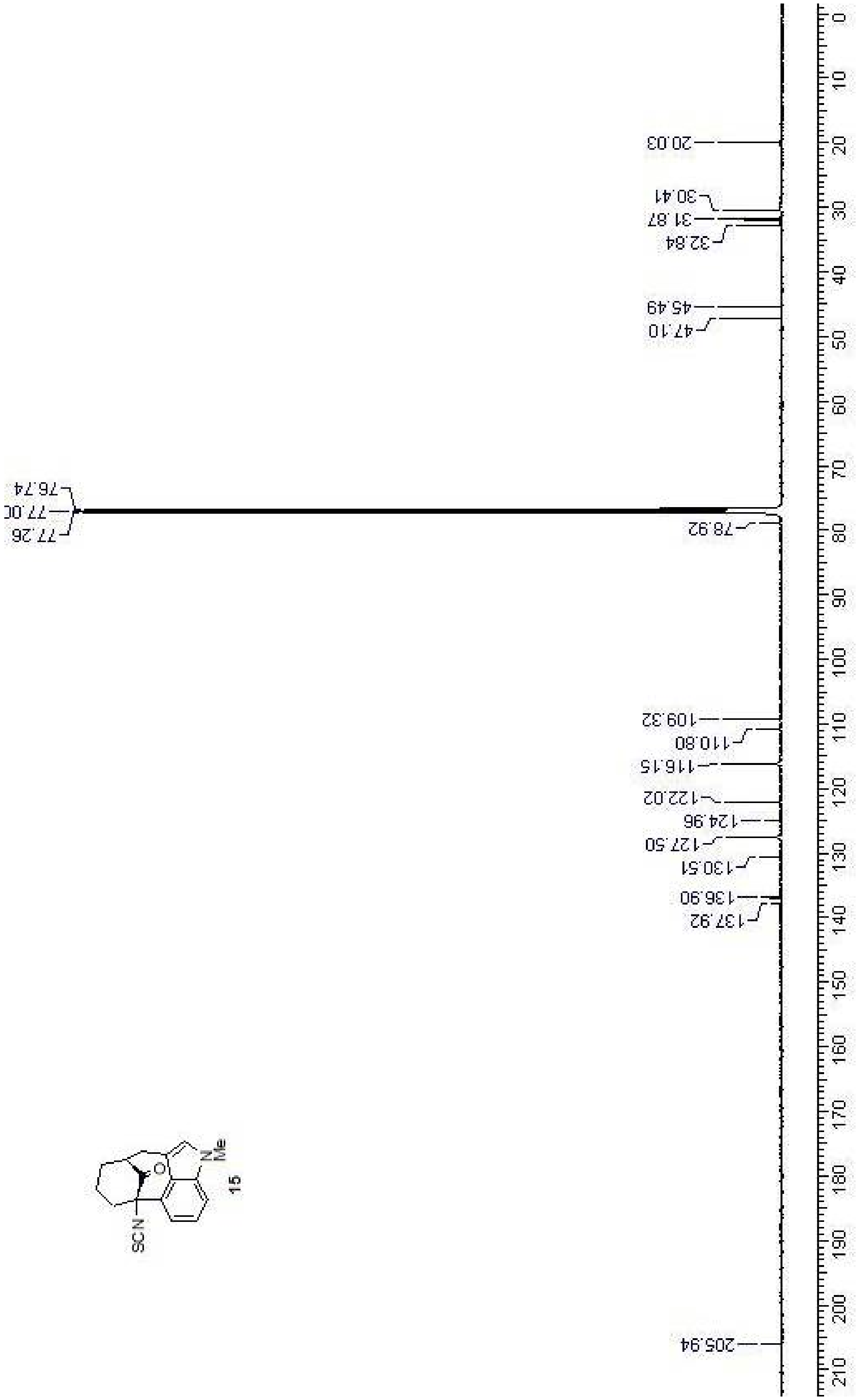

18.40
28.55
30.40
32.85
32.88
36.05
44.99
67.77
76.84
77.16
77.48
100.84
109.18
112.98
114.53
122.07
124.88
127.28
127.32
130.18
136.87
158.02
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
O
HN
N3
N
Me

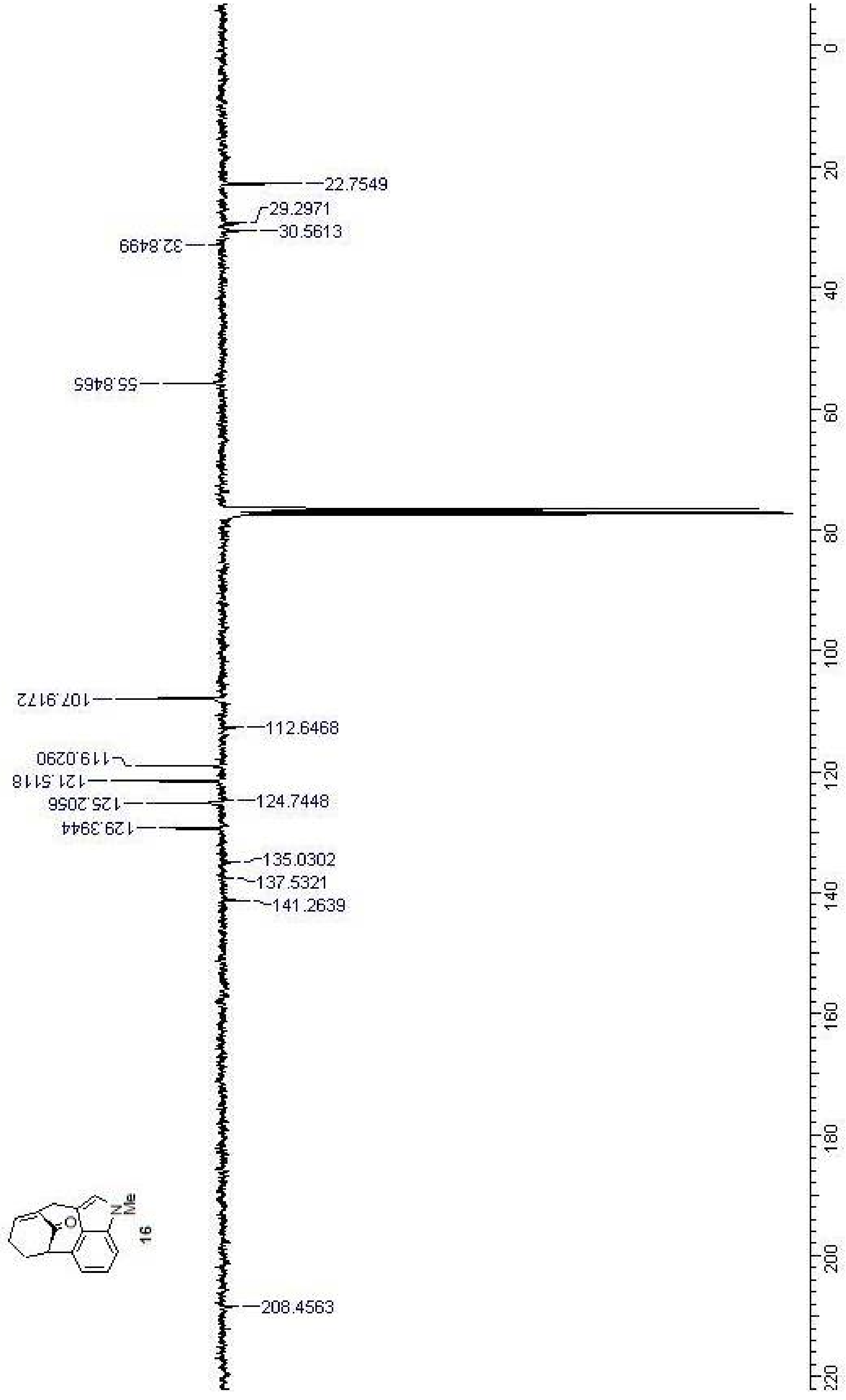
13

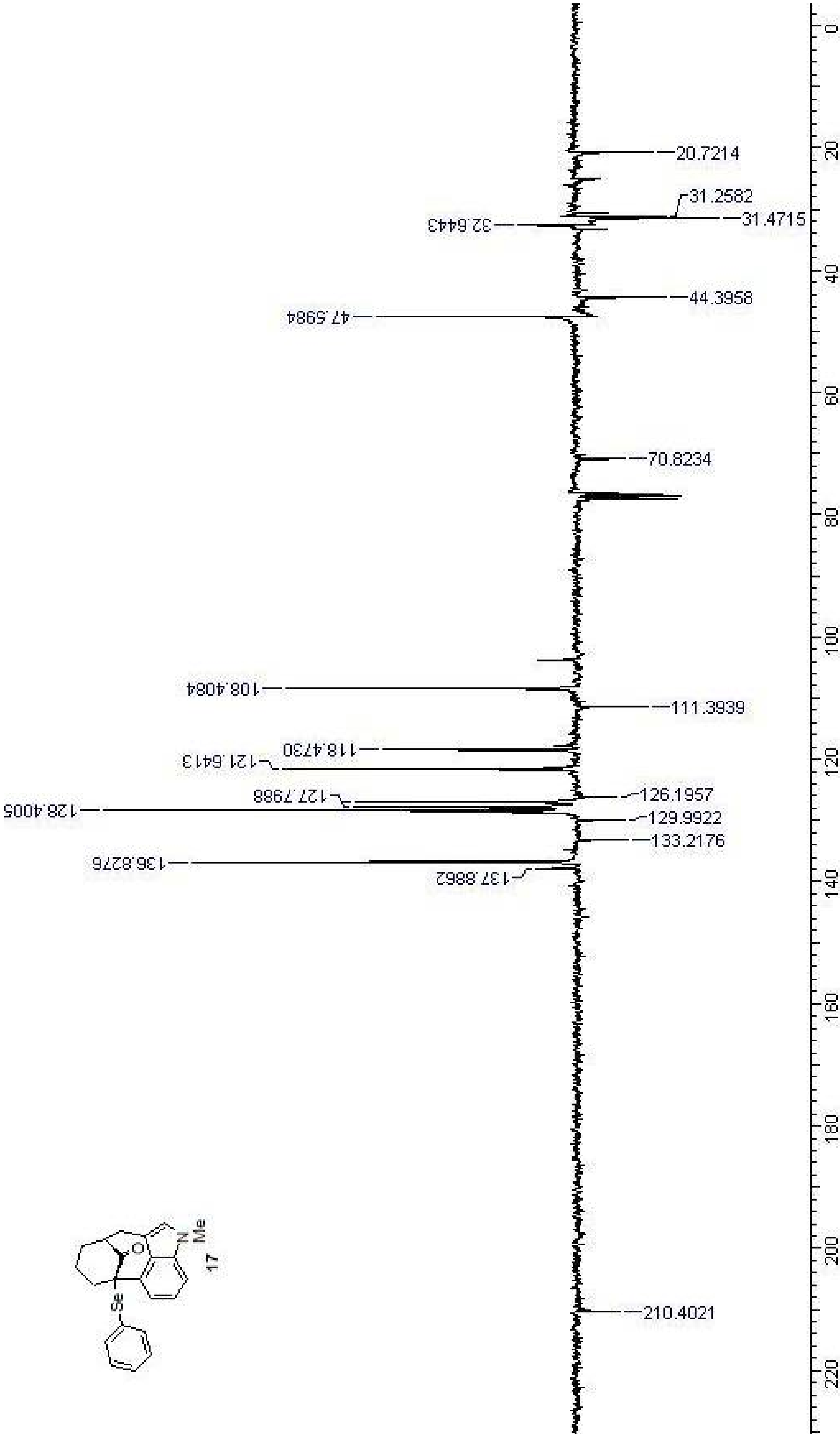

20.38
30.78
31.49
32.74
41.29
46.99
51.98
71.22
76.57
77.00
77.42
108.83
111.57
115.06
121.87
125.67
127.24
134.23
136.82
156.86
210.94
0
20
40
60
80
100
120
140
160
180
200
220
MeO
O
NH
O
N
Me

14

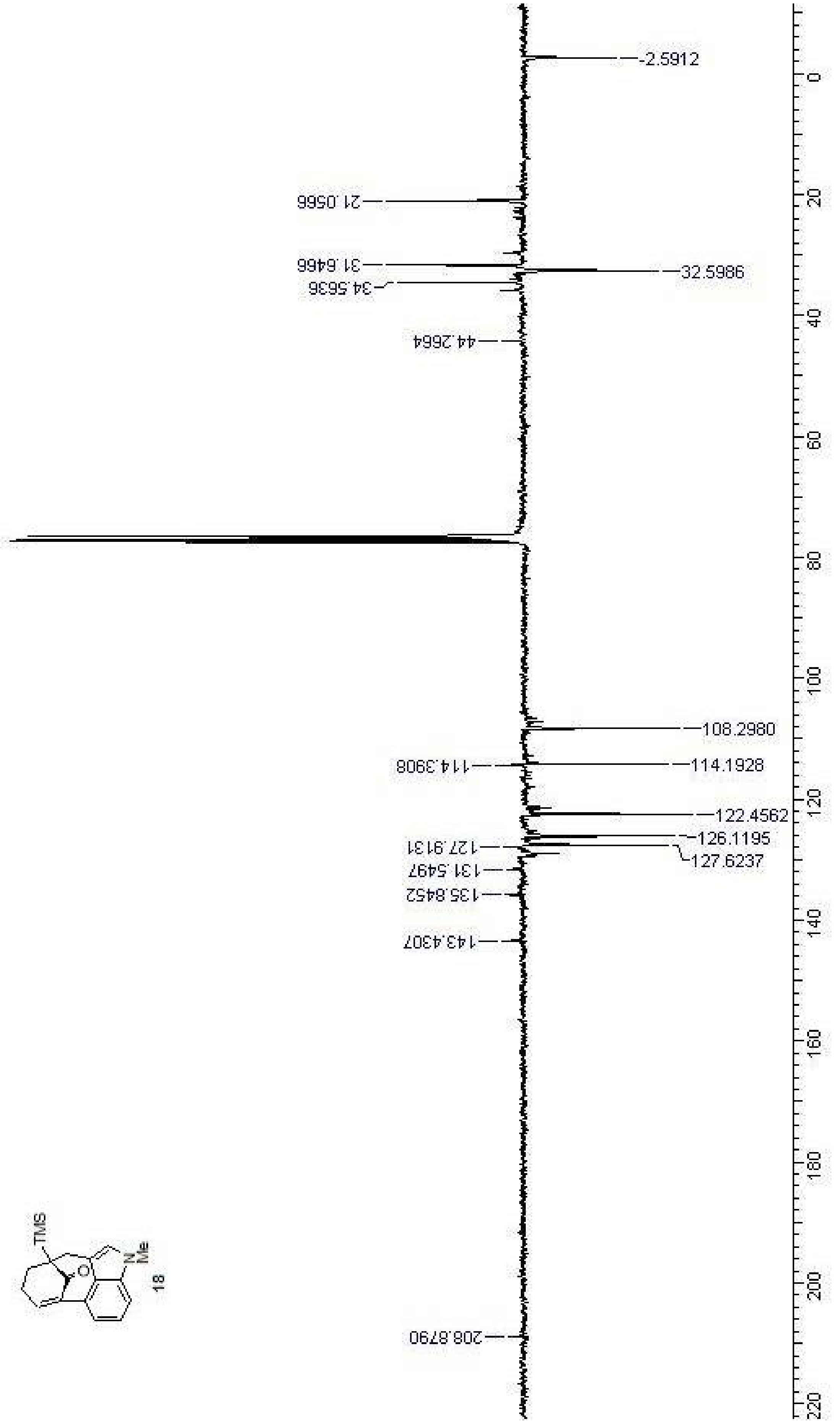

20.16
30.39
31.72
32.86
43.17
46.90
70.48
76.57
77.00
77.42
109.46
111.01
115.99
122.18
125.57
127.49
131.35
136.79
213.41
0
20
40
60
80
100
120
140
160
180
200
220
H₂N
O
N
Me

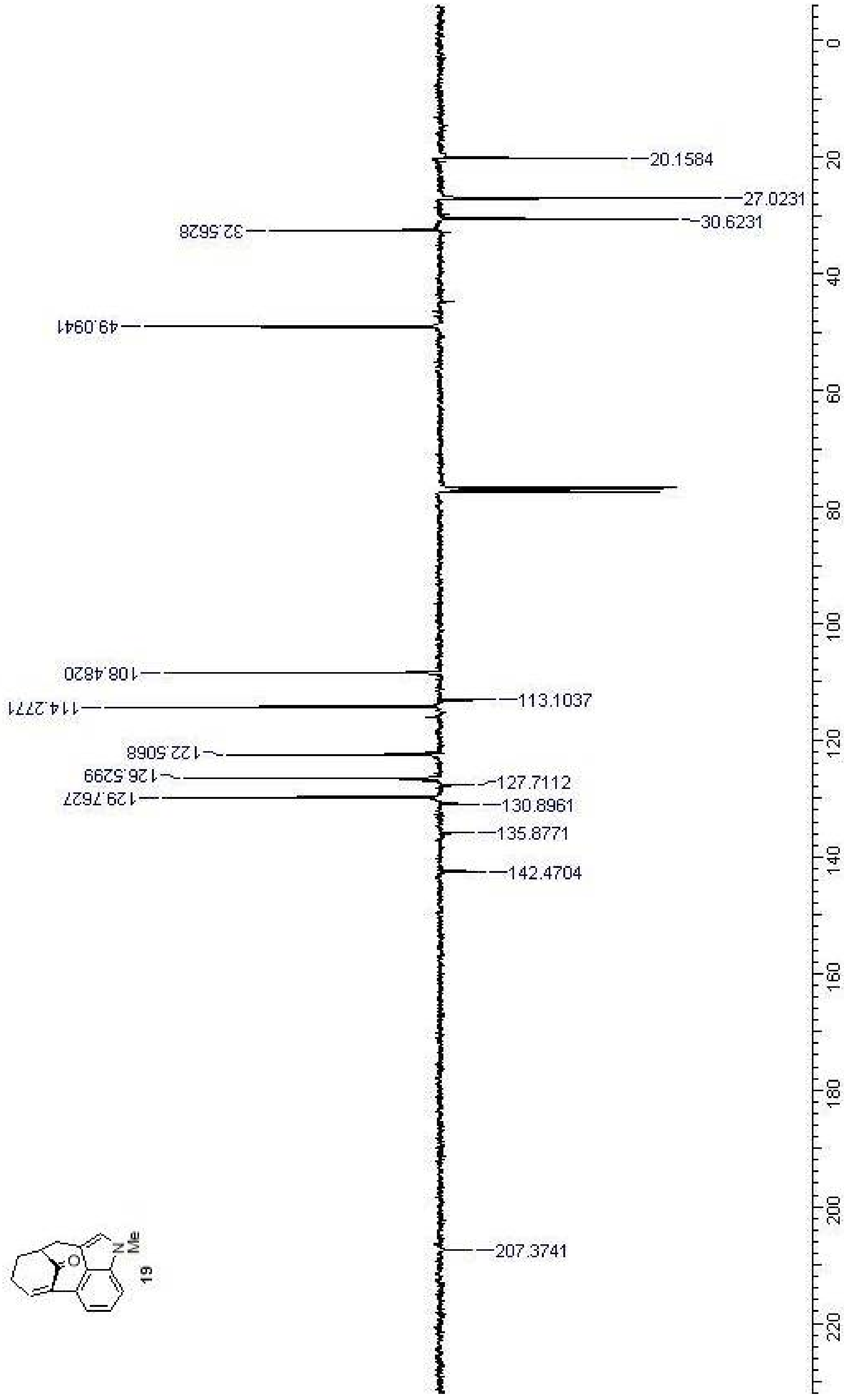

20.03
30.41
31.87
32.84
45.49
47.10
76.74
77.0C
77.26
78.92
109.32
110.80
116.15
122.02
124.96
127.50
130.51
136.90
137.92
205.94
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
SCN
O
N
Me
15

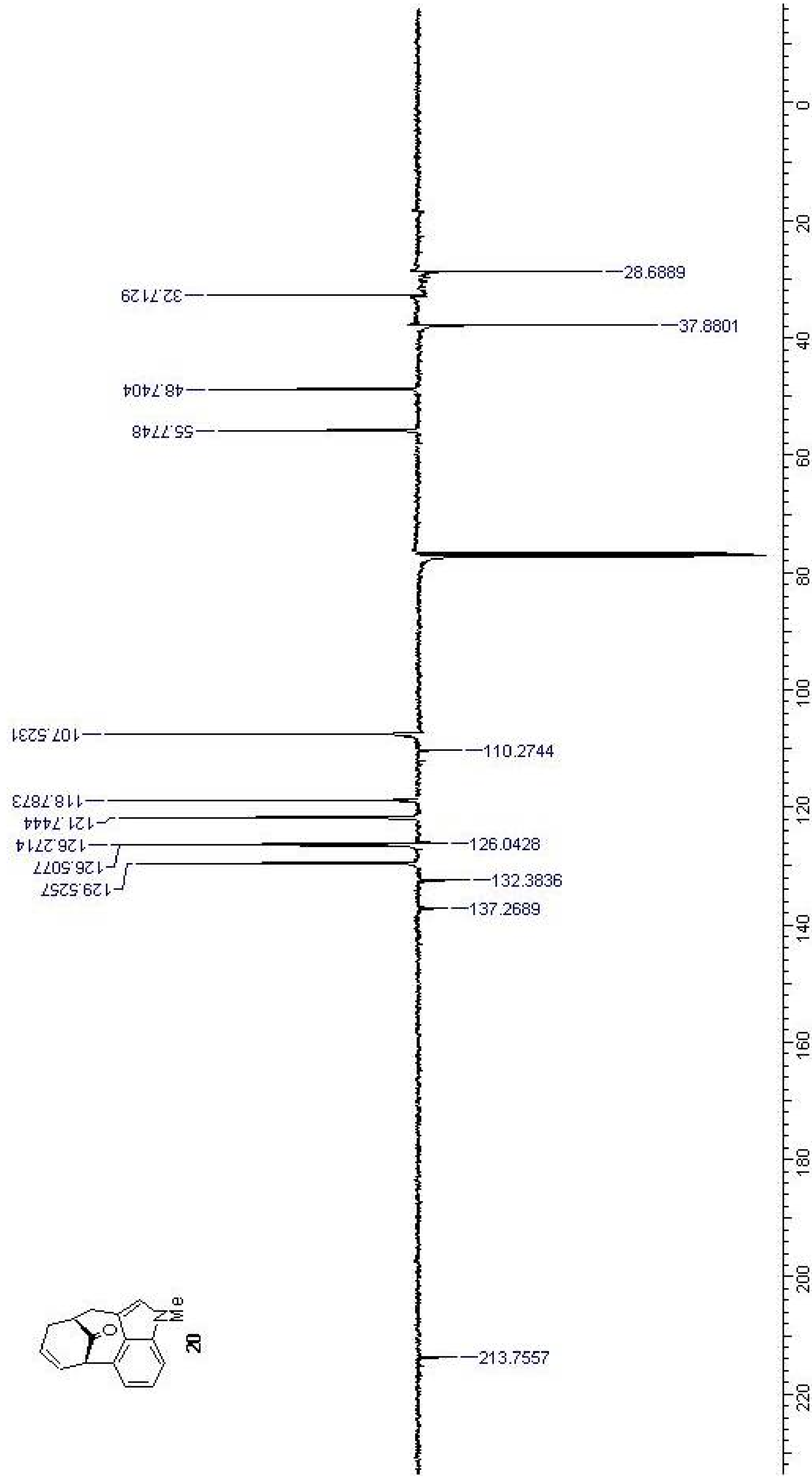

22.7549
29.2971
30.5613
32.8499
55.8465
107.9172
112.6468
119.0290
121.5118
124.7448
125.2056
129.3944
135.0302
137.5321
141.2639
208.4563
O
N
Me
16
0
20
40
60
80
100
120
140
160
180
200
220


20.7214
31.2582
31.4715
32.6443
44.3958
47.5984
70.8234
108.4084
111.3939
118.4730
121.6413
126.1957
127.7988
128.4005
129.9922
133.2176
136.8276
137.8862
210.4021
0
20
40
60
80
100
120
140
160
180
200
220
O
N
Me
Se

17


-2.5912
21.0566
31.6466
32.5986
34.5636
44.2664
108.2980
114.3908
114.1928
122.4562
126.1195
127.9131
127.6237
131.5497
135.8452
143.4307
208.8790
0
20
40
60
80
100
120
140
160
180
200
220
TMS
O
N
Me
18


20.1584
27.0231
30.6231
32.5628
49.0941
108.4820
113.1037
114.2771
122.5068
126.5299
127.7112
129.7627
130.8961
135.8771
142.4704
207.3741
0
20
40
60
80
100
120
140
160
180
200
220
O
N
Me
19


28.6889
32.7129
37.8801
48.7404
55.7748
107.5231
110.2744
118.7873
121.7444
126.0428
126.2714
126.5077
129.5257
132.3836
137.2689
213.7557
0
20
40
60
80
100
120
140
160
180
200
220
O
N
Me
20